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URINARY DISORDERS OCCURRING IN THE NEONATAL PERIOD

BY

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Urinary conditions with a distinctive clinical picture are not uncommon in newborn infants. The majority of infants show excellent response to treatment and early diagnosis is of great importance. In any circumstances it is difficult to obtain specimens of urine from these small subjects and the difficulties are frequently increased as a result of the anuria which is a common accompaniment of urinary disorders in its early stages. Usually the characteristic clinical features of these cases allow of a diagnosis being made and treatment being begun before examination of the urine has been possible.

It is the purpose of this paper to give an account of observations made on a series of sixty-one cases collected over a period of three years. Details are given of urinary findings in these cases as well as in a series of healthy newborn infants, clinical signs and symptoms are described, treatment is indicated and the results recorded. Autopsy findings are given in connection with certain of the fatal cases and details of progress after discharge from hospital in children who recovered.

Material.

Specimens of urine were obtained from newborn infants in the Royal Maternity Hospital and the Western General Hospital, Edinburgh. A large number were from healthy children and provided a control series. Of the sixty-one children with urinary infection fifty-two were born in the former and nine in the latter hospital: all were under observation from the time of birth. Twelve children included in this series attended the Infant Clinic in connection with the Royal Maternity Hospital and were examined at intervals for a period varying from seven months to two years. Of those not regularly attending the clinic twelve reported by request, fifteen were visited in their homes and replies to a questionnaire were received in connection with nine others. Four children could not be traced: nine died while still in hospital.

Method of examination of the urine.—Specimens of urine from female cases were obtained by catheter: in male infants they were collected in test-tubes attached to the penis unless required for bacteriological investigation when catheter specimens were employed. Microscopical examination of the urine was carried out as soon as possible after receipt of the specimen, which was thoroughly stirred but not centrifugalized. The high-power lens was employed throughout and the findings recorded in not fewer than fifteen fields in connection with each specimen. This method of examination was along lines suggested by Still[14] and Thomson[15].

The urine of the healthy newborn infant.

The urine of the newborn child differs from that of older subjects in that it may contain casts and cellular elements in the absence of disease in addition to certain amorphous and crystalline deposits[12]. In order to determine the normal microscopical findings in urine from newborn infants over two hundred specimens were obtained from healthy children whose ages ranged from twelve hours to fourteen days. Babies were selected who had been born spontaneously at term, had normal temperatures and were free from infection or disease as indicated by physical examination.

There were no cellular or other solid elements in one hundred-and-sixty-three of the specimens: cells or casts or crystals or various combinations of the three were found in the remaining forty-eight, all of which were obtained from children aged four days or less. Epithelial cells were the most frequent finding, varying in number from three to four in a field to one in fifteen to thirty fields: they were most numerous in specimens from female cases. Casts were found in twelve specimens from children less than three days old: they were never more frequent than one in ten fields. Ten specimens contained polymorphonuclear leucocytes: they never occurred in greater number than one in ten to fifteen fields. Isolated red blood cells were seen in occasional specimens. Amorphous urates and crystals of uric acid or oxalate crystals were present in the majority of urines obtained during the first few days of life: quantitative estimation of these was not possible but in none of the cases from which they were obtained were there granular deposits on the napkins.

Forty-three catheter specimens were examined bacteriologically. Thirty-three were sterile, seven gave isolated discrete colonies of b. coli on culture, in the remaining three sparse growths were obtained, in two of staphylococcus albus and in one of a non-haemolytic streptococcus.

Urinary findings in the present series.

The sixty-one cases included in this series presented characteristic clinical features described in detail later, which led to examination of the urine. The urines all differed from those examined in the preliminary investigation and the microscopical abnormalities fell into one of the following groups:—

(1) **Numerous pus cells** (fig. 1). In forty-eight cases of the series pus cells were present in each field in numbers varying from five to one hundred and forty: clumping of the cells was noted in a number of the specimens. Hyaline and granular casts (one to four per high-power field) were present in thirteen of these cases.

Discussing pyelitis in the newborn Sauer[13], Helmholz[5], Conrad[2] and others base their diagnosis on microscopical evidence of pus cells in the urine but do not indicate their frequency. Hoppe[8] points out that slight pyuria may be found in healthy children in the neonatal period but considers that the presence of more than five pus cells per low-power field

of an uncentrifuged specimen points to ' infection somewhere in the urinary tract.' Conrad[2] and Hoppe[8] mention the occurrence of clumping of cells and the latter considers that it is characteristic of infection.

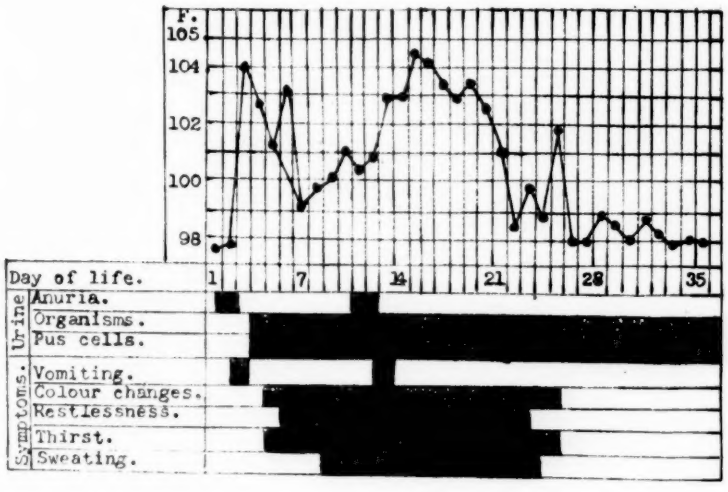

FIG. 1.—Male. Pyuria and bacilluria. Prolonged febrile course. Urine contained 15-30 pus cells per high-power field and was heavily infected with b. coli. Complete recovery: no history of recurrence of urinary symptoms at age 2 years 3 months.

(2) **Organisms in the absence of pus cells.** (fig. 2). Organisms were demonstrated in specimens of urine from three cases in the absence of pus cells. All three children were seriously ill, ran a high temperature and showed severe symptoms. The organisms could be seen in great numbers under the microscope and grew vigorously on culture: non-haemolytic streptococci and b. coli were cultured in one and pure growths of b. coli in two cases. Fresh specimens were examined from each case at intervals of one or two days.

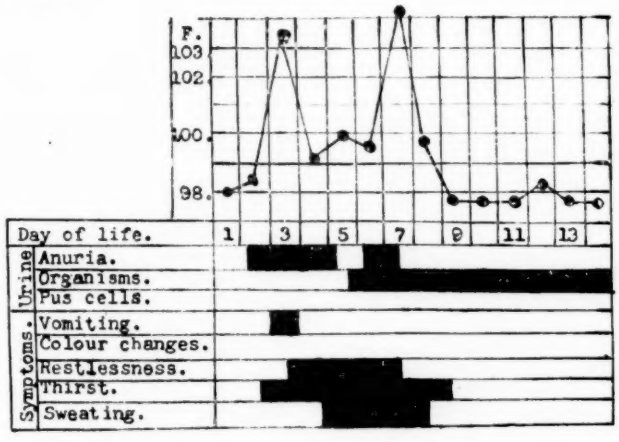

FIG. 2.—Male. Bacilluria. Catheter specimens of urine on 5th, 7th, 8th, 11th, and 14th days of life contained no pus cells but gave a profuse growth of b. coli on culture. Complete recovery: no history of recurrence of urinary symptoms at age 14 months.

Hoppe[8] emphasizes the need for repeated examination of the urine as even in the presence of infection pus cells may be absent in occasional specimens. In each of the above cases specimens were examined at intervals of twenty-four to forty-eight hours on at least four occasions. Helmholz and Millikin[6] consider that the urine of normal infants may contain a small number of organisms but they admit of the difficulty in excluding contamination. Ramsay[11] is of the opinion that in many acute urinary infections the urine contains epithelial cells and colon bacilli in greatly increased numbers but no pus cells.

The findings in connection with the bacteriology of the urine of healthy children agree with those of Helmholz. In the three cases referred to above massive infection limited to the urinary tract was associated with severe symptoms similar to those occurring in cases of established pyelonephritis: in this respect and in the absence of pyuria these cases resembled a number described by Ramsay[11]. This writer mentions b. coli as the infecting organism: in one of the present cases both streptococci and b. coli were present.

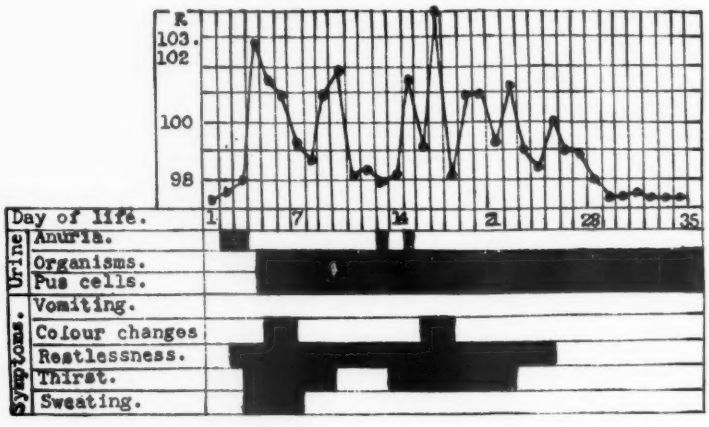

FIG. 3.—Female. Pyuria with mixed infection. Pus cells (5–15 per high-power field) present in all of nine specimens examined: on culture catheter specimens gave haemolytic streptococci and b. coli on the 5th, 18th, and 22nd days, and b. coli only on the 27th and 35th day. Complete recovery: no history of recurrence of urinary symptoms at age 11 months.

(3) Pyuria with mixed infection (fig. 3) was found in seven cases. B. coli were present in all seven: in four the accompanying organisms were non-haemolytic streptococci, in one b. pyocyaneous and in another haemolytic streptococci. In the seventh case specimens were obtained each alternate day: non-haemolytic streptococci and b. proteus were present in the first two: pus was not found until the third and b. coli were first cultured from the fifth specimen.

It is recognized that coliform infection of the urinary tract is the most common form: Thomson[15] however draws attention to the variety of organisms which may be found and Graham[3] considers that there is not such a predominance of coliform organisms in the newborn as in older children. The occurrence of mixed infection is not stressed in the literature but Helmholz[5] records a case in which the urine was infected by staphylococci.

(4) **Uric acid deposits in the absence of pus cells** (fig. 4). A heavy uric acid deposit on the napkin occurred in association with pyuria in fifteen cases. In five cases similar deposits were noted in the absence of pus cells in the urine: casts were present (one to four per high-power field) in four of these five cases. Culture of the urine gave a profuse growth of b. coli in each instance.

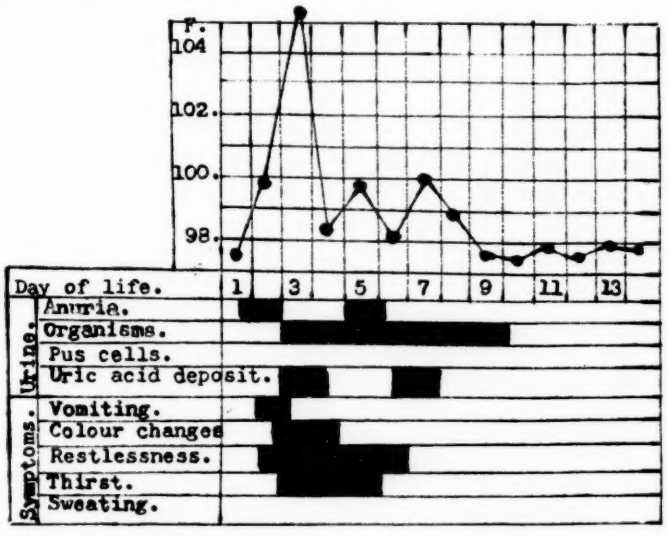

FIG. 4.—Female. Bacilluria with excessive uric acid crystal content of urine. Specimens of urine on the 3rd, 6th, 11th, and 14th days of life contained no pus cells. Short course, early disappearance of organisms. Complete recovery: no history of recurrence of urinary symptoms at age 18 months.

The clinical picture.

Table 1 gives a list of the clinical features met with in the present series and indicates the frequency with which they occurred. Individual signs

TABLE 1.

URINARY DISORDERS OCCURRING IN THE NEONATAL PERIOD: CLINICAL FEATURES AND THEIR FREQUENCY IN A SERIES OF 61 CASES.

CLINICAL FEATURES.	CASES. No.	CASES. PER CENT.
FEVER	49	80
ANURIA OR MARKED DIMINUTION IN URINARY OUTPUT	43	70
THIRST	43	70
RESTLESSNESS AND/OR IRRITABILITY	40	66
COLOUR CHANGES	39	64
SWEATING	36	59
VOMITING	31	51
COLLAPSE	12	20
OEDEMA	12	20
CONVULSIONS	6	10
ASSOCIATED CONDITIONS:		
A. INTESTINAL IRRITABILITY	10	16
B. POSTNATAL INTRACRANIAL DISTRESS	10*	16
C. MINOR SURFACE INFECTIONS	16	26

* The urinary condition occurred as a late complication in 9 of these cases.

and symptoms were absent in certain cases but never to such an extent as to result in the loss of its characteristic nature by the clinical picture. The usual finding was one of a slight febrile irregularity commencing about the second or third day of life in association with occasional vomiting or anuria or both. Subsequent symptoms and signs were usually more pronounced and took the form of great restlessness and thirst accompanied by profuse sweating. A few cases ran an afebrile course but in the majority the temperature was characteristically irregular and tended to be high on occasion. Colour changes were common. Sudden collapse occurred occasionally and convulsions rarely: oedema was sometimes a feature.

(1) **Onset.** Symptoms of great severity frequently occurred with startling suddenness though rarely as the first indications of disease. The onset was sudden in only nine cases in the series: in all the remainder initial signs were vague in character and gradual in development. Litchfield and Gillman[9] and Sauer[13] refer to the suddenness of onset as a characteristic of urinary infection in the newborn but other writers emphasize the variability of early symptoms.

Fever was the most common first symptom. In three cases described by Helmholz[5] fever was the only symptom and elevation of temperature was the first evidence of illness in six cases recorded by Graham[3] and two by Paterson[10].

Vomiting and diminution in urinary output were the symptoms next in order of frequency: Sauer[13], Litchfield and Gillman[9] consider that gastro-intestinal symptoms are usually the first evidence of infection and in two of three cases described by Conrad[2] diminished urinary excretion was the first feature.

(2) **The amount of urine.** Failure to pass urine either with normal frequency or in normal amounts was noted in the majority of the cases: this invariably occurred in the earlier days of the illness of which it was frequently the first evidence. It was not uncommon for the napkin to be merely moistened only once in the twenty-four hours and in several instances the interval was thirty-six hours or more. During the period of anuria there was no distension of the bladder and on the few occasions when the catheter was passed at the time, urine was not obtained. Later as diuresis was promoted polyuria was evident and persisted in convalescence, varying with the fluid intake. In fatal cases anuria was a striking feature during the terminal stages.

Von Reuss[12] draws attention to the limited urinary output during the first few days of life: he quotes Kotscharowski as finding thirty-four per cent. of newborn infants failing to pass urine in the first twenty-four hours but he himself considers that in health, micturition usually occurs two or three times during each of the first two days and increases in frequency until the end of the first week. There is little reference in the literature to the output of urine in the presence of infection during the neonatal period but in two cases of 'congenitally acquired pyelitis' Conrad[2] noted that severe symptoms were preceded by the passage of minute quantities of urine at lengthy intervals. The picture he describes closely resembles that found in a large number of the present series of cases.

(3) **Fever.** A rise of temperature was the most common initial sign: this was often only slight (99–100° F.) but, more characteristic than the height of fever was the persistence of an irregular temperature. The temperature varied taken at four-hourly intervals and showed a suggestive irregularity when charted only once daily (see fig. 4). The highest temperature recorded was 108° F. in a child who recovered: temperatures of 102° F. or over occurred in fifty per cent. of cases. The severity of the fever was not related to the duration of the illness: in the relatively few cases where onset of the illness was sudden and of a grave nature hyperpyrexia was present from the outset.

Fever was absent in eleven surviving and one fatal case (fig. 5): in all of these, abnormal clinical features were present and the urine contained pus and organisms. The apyrexial cases occurred in full-time and

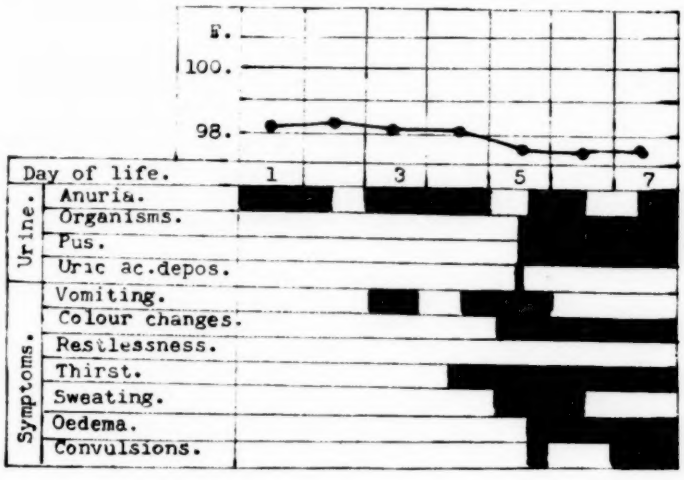

FIG. 5.—Female. Fatal case. Short afebrile course, characterized by only occasional passage of small amounts of urine, pyuria (54 pus cells per high-power field), terminal oedema and convulsions. Case 46.

premature infants: they tended to run a short course but in several instances the clinical features persisted for seven to ten days and the pyuria for several weeks.

Many workers consider pyrexia to be characteristic of urinary infection in the newborn and it is mentioned in connection with the majority of recorded cases. Hoppe[8] and Sauer[13] state that it is ' usually present ' but attention has not been drawn to those cases in which there is no fever. There is a divergence of opinion as to the height of fever usually present. Litchfield and Gillman[9] consider that it seldom exceeds 101° F.: Sauer[13] is in agreement although a temperature of 102·5° F. occurred in one, and of 104° F. in three of his series of fifteen cases: Ramsay[11] believes that high fever is characteristic. Cases described in the literature by Graham[3], Conrad[2], Paterson[10] and others indicate that temperatures of over 102° F. occur in about half their number: this is in agreement with the present findings.

(4) Vomiting occurred in fifty per cent. of cases and was not related to the severity of the other symptoms: it was absent in a number of the most severe cases. It took place during the early days of the illness and not infrequently was the first sign of disturbed health: it was rarely forcible and although occurring after every feed in a few instances usually took place only once or twice in the twenty-four hours. A striking feature was the cessation of vomiting which followed satisfactory diuresis even when other symptoms persisted for a longer period.

Of the twenty-eight cases recorded by Gueriot[4], Graham[3], Conrad[2], Sauer[13], Litchfield[9] and Paterson[10] vomiting was noted in thirteen. The nature of the vomiting was varied: in the majority it was only occasional, in one case it occurred after every feed and in another was projectile.

(5) Colour changes and collapse. Colour changes were characteristic: insidiously the face took on a dusky, grey appearance, not infrequently associated with a faint peri-oral cyanosis and a curious pallor of the scalp and forehead. At the same time a general limpness developed. This picture passed off as gradually as it developed, but while present, provided a striking contrast with the flushed skin, restlessness and irritability of the children at other times. In some cases changes of the nature described took place only on isolated occasions: in others they occurred frequently throughout the day during the height of the illness. They rarely occurred in the absence of fever and were noted in all fatal cases.

In a few cases the changes were more severe: there was sudden complete collapse, the skin was blanched, respirations were rapid and shallow, and the eyes were ringed and sunken. There was flaccid immobility of the trunk and limbs and a fixed expression of anxiety.

Thomson[15] and Still[14] describe attacks of collapse accompanied by colour changes and unexplained fever in older children as being suggestive of pyelitis. Dealing with the newborn infant Sauer[13], Conrad[2], Litchfield[9] and others remark upon the pallor and anxious faces sometimes met with in the presence of urinary infection.

(6) Restlessness and irritability were characteristic of a large number of the children in the series. The restlessness was continuous over long periods and consisted of impetuous movements of head and limbs and ' squirming ' of the body: in certain cases it developed into an actual fury, the child snatching at, and chewing, the bed covers. Restlessness frequently preceded elevation of temperatures: it was also met with in the absence of fever. It lessened in severity as the illness ran its course, often disappearing with surprising suddenness. As restlessness diminished irritability became more pronounced: unaccustomed to rationing of fluids during the height of the illness these children resented discipline and their cry of thirst became an imperious bellow. In contrast with the more usual state of agitation a few cases were limp and inert: the course run by these infants was never stormy, tended to be protracted, and was not characterized by high fever.

Still[14] draws attention to the extreme restlessness and misery found in older children suffering from pyelitis and Graham[3] stresses their importance in the diagnosis of the condition in the newborn: both writers mention drowsiness and lethargy as occasionally occurring and Still considers that they point to a severe infection.

(7) **Thirst** was a feature of the majority of cases: it was always intense and in their desperation for fluids the children impetuously chewed their teat or 'gulped' down their fluids. Thirst was noted in the absence of fever but more commonly its appearance coincided with the initial rise of temperature; it was a constant accompaniment of fever but persisted for a considerable time after final settlement of the temperature.

(8) **Sweating** did not occur in the absence of fever and was usually accompanied by thirst: it was not affected by variations in the urinary output. Sweating usually occurred at the height of the illness: it was always profuse and the presence of beads of perspiration standing out on the forehead and scalp was characteristic of a number of cases.

(9) **Oedema.** Urinary abnormalities were found in only a small proportion of newborn infants showing oedema, and oedema was present in only twelve of the sixty-one cases of the present series. It was invariably preceded by marked diminution of urinary output and was present before death in five of the nine fatal cases. It occurred in one of the cases with severe urinary infection but no detectable pyuria, and in four cases where there was a heavy napkin deposit of uric acid and coliform infection of the urine but no pyuria. In males oedema first appeared in the suprapubic region and in females in the labia: the lower limbs were the next commonest site and in the most severe cases it was also found in the lumbar region, around the eyes and on the dorsal aspect of the hands. Appearing somewhat suddenly, oedema gradually disappeared following diuresis.

(10) **Convulsions** were uncommon but of grave significance. In five of six cases in which they occurred death followed the first fit within twenty-four to forty-eight hours. The fits in these cases were of a violent nature, involved the entire body, were accompanied by temporary unconsciousness and took place during periods of prolonged anuria. In the sixth case the infant was two days old and had not passed urine since birth when sudden, generalized spasticity was followed by slight clonic movements of the hands and face: a specimen of urine obtained a few hours later contained large numbers of pus cells. The child eventually recovered.

Thomson[15] and Holt[7] refer to the relatively rare occurrence of convulsions in children suffering from pyelitis: Thomson found that they were more prone to occur in young babies and Holt that they were associated with severe infection. Dealing with urinary infection in the new-born Sauer[13] mentions convulsions as one of the less common findings: they occurred in two of three cases recorded by Conrad[2] and in one of them were related to periods of diminished urinary output.

(11) **Remissions** occurred in a limited number of cases but only in one instance on more than one occasion: they occurred with the same frequency in the two sexes. Of more frequent occurrence were deceptive periods when symptoms improved and the temperature settled temporarily, only to

become worse again after noticeable diminution in the urinary output (see fig. 3). No recurrence of symptoms occurred in any of the children followed up after discharge from hospital.

Holt[7], Thomson[15] and others remark upon the frequency of relapse in cases of urinary infection in children. Holt states that fever may be interrupted by periods of normal temperature lasting several days and he considers that recurrence of symptoms may take place a few weeks to several years after the initial illness. Return of fever and symptoms after the condition had apparently settled was noted in two cases of neonatal pyelitis by Graham[3]: he also followed up two cases, one for a period of four months and the other for six months but in neither was there a relapse.

Associated conditions.— 1. INTESTINAL IRRITABILITY. In ten cases of the series frequent, green foetid, motions containing a large amount of mucus were passed; in six the presence of abnormal motions was first noted two to three days after the detection of pyuria; in two the alimentary disturbance preceded the urinary condition by forty-eight hours and in the remaining two upset of urinary and bowel function occurred simultaneously.

Discussing pyelitis in children Thomson[15], Still[14], and Holt[7], draw attention to the fact that the condition may either follow or accompany gastro-intestinal symptoms. No mention is made of the stools in a number of the recorded cases of neonatal pyelitis but while Litchfield[9] and Sauer[13] are of the opinion that gastro-intestinal symptoms are common and usually appear before the pyelitis is discovered Graham[3] emphasizes the absence of diarrhoea in all of the six cases described by him.

2. POSTNATAL INTRACRANIAL DISTRESS. Urinary infection occurred as a late complication in nine cases which had shown symptoms of cerebral haemorrhage following delivery (fig. 6). Specimens of urine obtained during

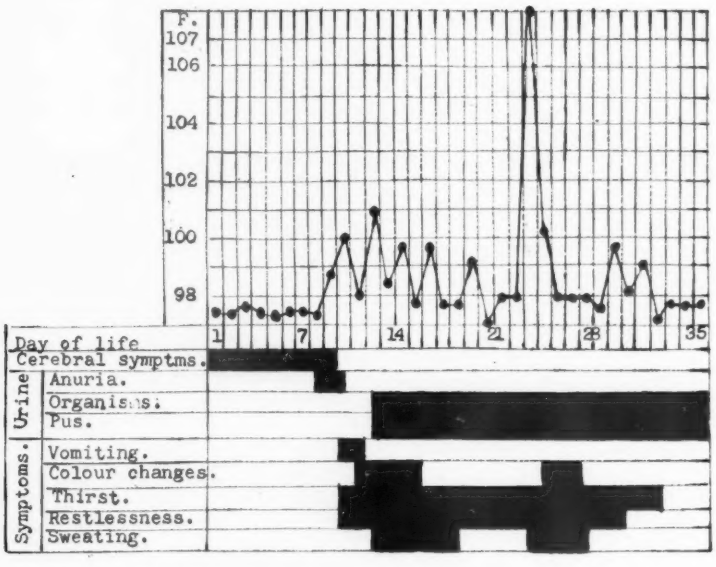

FIG. 6.—Female. Pyuria and bacilluria as a complication of intracranial birth trauma. Specimens of urine on the 4th, and 7th days of life contained no abnormalities and were sterile on culture: b. coli and pus cells (8–14 per high-power field) present in specimens on the 10th, 16th, 25th, and 34th days. Complete recovery: no history of recurrence of urinary symptoms at age of 1 year 10 months.

the period of intracranial distress were normal: pyuria or bacilluria or both first occurred from the sixth to the eleventh day of life. Apart from the late development, the urinary condition ran a course similar to that of other cases in the series both with respect to symptoms and variability of duration. One of the nine children died and details of post-mortem findings are given on page 348 (case 14).

3. Minor surface infections. Weakened resistence to infection was evident in a number of patients whose illness had run a prolonged course. In these children sweating gave rise to a papular rash which frequently became pustular: the nose, eyes, and mouth were other common sites of low-grade infections.

Duration of the illness.— In almost every case abnormalites persisted in the urine for a varying period after the disappearance of symptoms and a number of children were discharged from hospital before the urine had become normal. Severe symptoms persisted from a few days to six weeks: they were not inevitably associated with a prolonged course, but symptoms persisting over a number of weeks were always severe. The duration of the illness was not related to the sex of the individual: in cases where mixed or unusually heavy b. coli infection was found the illness was severe and protracted. Cases in which the symptoms were persistent were also the cases in which bacteruria or pyuria remained longest after the disappearance of symptoms: several children had pus in their urine for seven or eight weeks after an apparently complete clinical recovery from a critical illness.

According to Holt[7] the duration of an attack of acute pyelitis may vary from a few days to six or eight weeks and pyuria may persist for a much longer time. Recorded cases indicate that Holt's views apply equally well to the neonatal as to any other period in childhood: Litchfield[9] and Sauer[13] both give six weeks as the usual duration of illness in the newborn but Graham[3], Gueriot[1] and Conrad[2] describe cases in which symptoms disappeared in the course of a few days. There is general agreement among these and other workers that pyuria tends to persist for a considerable time after the disappearance of symptoms.

Further progress.—Nine children died never having left hospital. Recovery was complete as measured by the disappearance of symptoms in all remaining fifty-two cases prior to their discharge. Contact was lost with four children after they left hospital. Forty-eight children were followed up in their homes and at the Royal Maternity Hospital Infant Clinic for periods varying from seven months to over two years: in no single instance was there a return of symptoms referable to the urinary tract: mental and physical progress was normal in all these children and the occurrence of neonatal urinary infection had not interfered with their later development.

Fatal cases.

Nine cases proved fatal and the following are their main clinical features together with autopsy findings when permission was obtained for post-mortem examination.

Case 2. Male (full-term, normal delivery). The baby showed a satisfactory condition for two days, on the third day refusing feeds, vomiting twice and not passing urine. On the fourth day there were sudden fever (101° F.), colour changes, thirst, with later complete collapse. Urine was passed after 36 hours' interval (20 pus cells per high-power field), T. 101° F. to 103·8° F. On the fifth day thirst, sweating, restlessness, pallor and collapse on two occasions occurred. T. 101° F.–102·8° F. He died in convulsions in the evening. No post-mortem examination was permitted.

Case 8. Male (twin, premature, weighing 2 lb. 12 oz.). Born by Caesarian section for placenta praevia. Showed a moderately satisfactory condition for two days. On the third, fourth and fifth days there was occasional vomiting. On the sixth day occasional vomiting occurred, no urine was passed and suprapubic oedema was noted. On the eighth day, there was increased oedema with vomiting, T. 105° F., marked bacilluria and pyuria (10 per high-power field) and thirst. On the ninth day no urine was passed. On the tenth day, T. 104·8° F., urine was passed, pyuria (14 per high-power field) was noticed, the oedema was less and colour changes occurred. On the twelfth day, return of oedema and frequent green motions were noted leading to death. Post-mortem examination (48 hours after death) showed the kidneys congested at boundary zone. Microscopically there was extensive post-mortem autolysis, pelvis healthy.

Case 14. Female (full-term, high forceps delivery), was asphyxiated at birth, but there was no superficial bruising at site of forceps application. Symptoms of severe intracranial distress were present from second to fourth day, with convulsions and fever and two urinary examinations were negative. The cerebral condition settled by fifth day the child being weak and exhausted. On the seventh day, anuria, fever and occasional vomiting occurred. On the eighth day there was sweating and urine was passed once. On the ninth day, T. 100–105° F., pyuria (25 per high-power field) and bacilluria, colour changes, oedema, great thirst and restlessness occurred. The condition remained unchanged with great fluctuations of temperature until thirteenth day when the child collapsed following a convulsion. Death occurred on fourteenth day. At autopsy, a tentorial tear and subdural haemorrhage were found with clotted blood in posterior fossae of base of skull. The kidneys showed intense congestion of the apices of pyramids, and microscopically, dilated collecting tubules, containing a number of polymorphonuclear leucocytes and infiltration of interstitium by polymorphonuclear leucocytes in localized patches.

Case 31. Male (full-term, normal delivery), showed a satisfactory condition for two days. On the third and fourth days he was restless with a whining cry, T. 98·8°–99·4° F. On the fifth day, rapid respirations, marked pallor, extreme restlessness and great thirst were noted with T. 105° F., and in the urine, 140 cells per high-power field, numerous casts and coliform organisms. On the sixth day, vomiting and frequent green motions were present and T. 103°–105° F. Otherwise there was no change. On the seventh to fifteenth day the condition persisted. The baby became irritable and gradually weaker, with frequent colour changes, extreme thirst. The urinary findings were unchanged,

but an extensive pustular skin condition developed. T. 101° to 105° F. Death took place on the fifteenth day. No post-mortem examination was allowed.

Case 32. Male (premature, weighing 2 lb. 3 oz., normal delivery). His frail condition was maintained during first three days. On the fourth day, he did not pass urine, T. 99° F. There was suprapubic oedema, and he was refusing feeds. On the fifth to tenth day he passed small amounts of urine at long intervals, becoming restless, with great thirst, T. 98·8°–99·4° F. On the eleventh day, urine was passed once daily and there was pyuria (14 per high-power field), bacilluria, fretfulness, sweating and colour changes, T. 101° F. On the twelfth to fifteenth day, he was getting weaker with severe turns of collapse and terminal green motions. Death occurred on fifteenth day. No post-mortem examination was allowed.

Case 33. Female (full-term, difficult breech extraction with forceps to after-coming head). Facial paresis was noted. On the first day her condition was satisfactory and she passed urine. On the second day no urine was passed. The labia were swollen and the baby was fretful and restless. On the third day, urine was passed after 40 hours' interval and contained pus (12 per high-power field), a few red blood cells and numerous coliform organisms. Sweating and marked pallor were noted, T. 100° F. On the fourth day she passed large amounts of urine, T. 99·5° F. The pyuria remained much the same, the oedema less and thirst and pallor persisted. From the fifth to eighth day the clinical condition improved and there was a diminution in pus cells in urine. On the eleventh day, T. 104·6° F., there was vomiting, an apprehensive expression, nystagmus, and the picture of intracranial distress. On the thirteenth day, the diagnosis of intracranial haemorrhage was confirmed by lumbar puncture findings; the urine still contained pus (10–15 per high-power field) and coliform organisms. Death took place on nineteenth day. Post-mortem examination showed an intraventricular haemorrhage with gross destruction of brain substances. There was marked hyperaemia of the apices of the renal pyramids, uric acid deposits in straight tubules. Microscopically, the collecting tubules of kidney contained a number of pus cells and debris, uric acid deposits in the straight tubules, but no inflammatory infiltration and the pelvis was healthy.

Case 43. Male (full-term, normal delivery), had slight asphyxia at birth. During first two days his condition was satisfactory: he passed urine once in 48 hours. On the third day, blood stained vomiting occurred, and the baby became exhausted, with grey colour and diarrhoea. On the fifth day, vomiting of bright red blood occurred and no urine was passed for 48 hours. T. 100·6° F. There was some tenderness in left abdomen, with sweating and thirst. On the sixth day foetid motions were passed and only a small amount of urine (14 pus cells per high-power field, occasional red blood cells, bacilluria). Oedema and turns of collapse developed, but there was no sickness. T. 100–104·4° F. On the seventh day, the condition was weaker with cyanotic turns, physical signs suggestive of pneumonia and occult blood in stools, T. 102–104·8° F. He gradually sank, with coarse twitching movements of extremities and small subcutaneous haemorrhage in cheek, T. 100–102° F. Death occurred on ninth

day. The post-mortem findings were a 'horse shoe' kidney, with some degree of hydronephrosis as result of pressure on the pelvis, and pneumonia. Microscopical examination of the kidney tissue showed structure developmentally normal, with extreme congestion at apex of pyramids, and haemorrhage into stroma. Many collecting tubules were dilated, containing debris, epithelial cells, occasional polymorphs. There were several small interstitial haemorrhages, but no interstitial inflammatory infiltration.

Case 46 (fig. 5). Female (normal delivery, premature, 5 lb. 0½ oz.). Her condition was satisfactory for two days. On the third day, no urine was passed, and she was thirsty, restless and jaundiced. On the fourth day, pyuria (50 pus cells per high-power field) was noted with numerous coliform bacilli, the urine was passed once in 36 hours. On the fifth day periods of grey pallor and two convulsions occurred with thirst and uric acid napkin deposits. T. 98·0° F. On the seventh day, T. 97·2° F., the baby was collapsed with definite anaemia. At post-mortem examination there were no definite findings beyond general anaemia, and congestion of kidneys with uric acid infarcts. Microscopical examination of kidney tissue showed intense congestion of tips of pyramids, great dilatation of ducts and dense, diffuse infiltration of interstitium by masses of polymorphs. Polymorphs present also in tubules. There was suppuration with necrosis and disappearnce of epithilium of pelvis with inflammatory cells in lumen.

Case 48. Male (full-term, normal delivery). His condition was excellent during first few days and weight was on the increase. On the sixth day, occasional vomiting was noted, T. 98–102·8° F. On the seventh day he was still vomiting with sweating, intense thirst, rapid respirations and collapse in evening. On the eighth day, loose offensive stools and frequent colour changes occurred, T. 99–100° F. On the tenth day, no urine was passed for 48 hours and there was doubtful resistance to palpation in the right kidney angle. On the eleventh day, pyuria (45 cells per high-power field) was noted. T. 105° F. He was passing large amounts of urine, otherwise there was no change. On the thirteenth day, urine was passed once in 48 hours, T. 100–102° F. There were extreme colour changes and frequent vomiting, occasionally forcible with oedema and a convulsion in evening. On the fifteenth day, a septic skin and mouth condition was noted leading to death. At post-mortem examination the macroscopic findings were indefinite beyond partial atelectasis. Microscopic examination of kidney tissue showed groups of collecting tubules containing pus cells, the condition not being widespread and the areas affected small. There was no interstitial inflammatory infiltration but great congestion especially at apices of pyramids.

Six autopsies were carried out. Post-mortem degeneration of the tissues was so advanced in one of them that microscopic examination was valueless. The complete histological picture of early suppurative pyelonephritis was present in one case (no. 46). The findings in the remaining five cases were limited to the presence of pus cells in dilated collecting tubules and intense congestion at the apices of the pyramids: in addition, early leucocytic infiltration of the interstitium was present in one and interstitial haemorrhages in another. Uric acid infarcts were noted in two cases. Grossly abnormal development of the kidneys characterized one case.

Discussing the findings in cases coming to autopsy with a clinical diagnosis of pyelitis Hoppe[8] remarks upon the frequency with which pathological changes are entirely absent or are located in the kidney substance and not in the pelvis. He draws attention to the danger if autopsy is delayed of post-mortem autolysis rendering microscopical examination of kidney tissue valueless. Still[11] is of the opinion that although kidney involvement is often present in fatal cases of pyelitis there is no associated nephritis in the majority of those that survive. Holt[7] on the other hand considers that in severe cases some degree of pyelonephritis is present: this he contends may take the form of degeneration or only collections of either polymorphonuclear leucocytes or small abscesses in the renal parenchyma.

Treatment.

Breast feeding was employed where the child's condition remained good and provided there were no signs of collapse and that high fever was not present. Where breast milk was either not available or not desirable, feeds were of cow's milk, skimmed, sweetened and diluted. Extra fluids in the form of water and weak tea were given between feeds and in the presence of collapse or hyperpyrexia these fluids were given at hourly or half-hourly intervals and milk temporarily excluded. The tea, while helping to lessen the thirst, had a definite diuretic effect and possibly acted as a mild stimulant.

Alkalies were given in the form of sodium or potassium citrate. An initial dose of 16–20 grains in twenty-four hours was usually employed: in a number of cases this sufficed to alkalinize the urine but in others as many as 60–80 grains daily were required before the reaction of the urine changed. Dosages were then adjusted in order to maintain alkalinity. In several cases the clinical condition showed marked betterment and the temperature fell before the urine had become alkaline: in two cases recovery was complete although the urine never became alkaline. Among the cases followed up after their discharge from hospital a considerable number continued to pass acid urine containing pus and bacteria for a number of weeks without there being any return of symptoms.

Attention was paid to bowel function and regular evacuation aimed at: an initial dose of castor oil (30 minims) was given as a routine and where intestinal irritability was a feature small doses of a paraffin preparation were prescribed (e.g. Emuls. petrol. B.P. 30 minims three times a day). When the motions were foetid or contained mucus, bowel lavage was carried out daily.

In the severe cases local warmth was applied to the loins in the form of an antiphlogistine poultice and this appeared to have a distinctly beneficial effect on kidney excretion. Where colicky pain was present relief was afforded by carrying the poultice over the abdomen.

Tepid baths were given when there was maintained hyperpyrexia and small repeated doses of brandy used as a stimulant.

Discussion.

The observations indicate the characteristic nature of the clinical picture in urinary disorders occurring in the newborn. There was a striking similarity in the signs and symptoms in all the cases. Infection of the urine was demonstrated in each instance but the microscopical abnormalities in the urine were varied. In several instances symptoms occurred before the appearance of abnormalities in the urine and in a large number of cases bacteruria and pyuria persisted for many weeks after the disappearance of symptoms. Symptoms were closely related to the excretory activity of the kidneys: aggravation of symptoms coincided with diminution in urinary output and improved with successful diuresis. It is possible that the initial occurrence of symptoms of general distress and of secondary urinary infection were contributed to by factors further limiting the small amount of concentrated urine normally associated with the early days of life.

In children suffering from intracranial birth injury, symptoms arising from urinary infection occurred later than in other cases: this late incidence may have been contributed to by the diminished urinary excretion resulting from lessened fluid intake and sedative treatment. The occurrence of urinary complications in these cases is not common. The nine cases described represent a small percentage of cases of cerebral birth injury seen during the period of these investigations. Apart from children with injuries of this sort the nature of the delivery did not appear to contribute towards the urinary condition: thirty-seven were spontaneously delivered, forceps were used in twelve and Caesarian section was performed in two.

The majority of the recorded cases of urinary infection in the newborn are in males, a fact which Conrad[2] emphasizes when describing three cases in girls. The figures of this series, forty males and twenty-one females (or thirty-five and sixteen respectively, after eliminating cases complicated by an earlier cerebral condition), indicate that urinary disorders may occur in newborn children of either sex. Conrad[2] suggests that infection is ' congenital ' and in support of this quotes two instances of pyelitis in newborn children whose mothers suffered from the same condition during pregnancy. Such a theory does not completely explain the one instance in the present series of urinary infection in both mother and child, as in the former the organism was a streptococcus and in the latter b. coli. Infection of the urine by spread from the alimentary tract has always been considered as likely. In the present series grossly abnormal stools were passed in ten cases. In two of these the sequence of events consisted of a particularly severe stomatitis with a secondary involvement of the bowel followed by urinary infection: in the remaining eight cases urinary and alimentary disturbances occurred within a short period of one another. These cases do no more than suggest the possibility of a common source of infection and in the remaining fifty-one cases of the series there was no clinical evidence pointing to the bowel as a source of the urinary infection.

According to Addison[1] congenital abnormalities account for a considerable number of cases of pyuria in older children but they contributed to only one fatal result in the present investigation (case 43). This was the only example of a developmental error of the urinary tract encountered in over two hundred consecutive post-mortem examinations on newborn infants. It is significant that among autopsies carried out on older subjects three children with hydro-ureter and hydronephrosis all died at the age of five months.

Post-mortem findings in the present investigation demonstrated that pathological changes were limited to the urinary tract (apart from the cerebral haemorrhage in cases 14 and 33), and with the exception of one case (46) were confined to the kidney substance. The changes were usually slight and it is justifiable to assume that they were even less so in surviving cases: the unlikelihood of there being any permanent morbid changes is borne out by the complete recovery noted in connection with all these cases.

The results obtained in the present series indicate that alkalies are as effective in the newborn as in older children and they also favour the view that the value of alkalies is their diuretic action. The chances of recovery are good. Prognosis must be guarded until satisfactory diuresis is attained, more particularly where there is persistent oedema, however slight. Convulsions are of grave significance and if associated with anuria are likely to be followed by death. The height of the fever is of little prognostic value: there may be no rise of temperature in even the most serious cases. The duration of the illness varies from one to many weeks and convalescence is frequently protracted. Recovery is usual and it is always complete.

Summary.

1. The abnormal microscopical and bacteriological findings in the urine of sixty-one newborn children with urinary disorders are described and details given of the clinical signs and symptoms. The urinary findings are compared with those in a series of healthy newborn children.

2. The abnormalities present in the urine were varied. Organisms were present in every case, pus was present in large amount in fifty-three cases: excessive deposits of uric acid and urates were noted in twenty cases, in five of which there was no pyuria.

3. A characteristic clinical picture is found in association with urinary conditions in the newborn. Onset of the illness is usually indefinite: prolonged anuria, especially when accompanied by fever or occasional vomiting is suggestive of a commencing urinary condition and justifies immediate diuretic treatment. Later restlessness, thirst and sweating develop and colour changes are characteristic of the illness at its height. Collapse occasionally occurs: high fever is common but a few cases run an afebrile course. Convulsions are of grave significance.

4. Symptoms are closely related to the excretory activity of the kidneys and treatment should be directed towards the promotion and maintenance of adequate diuresis. This is best attained by the giving of fluids at frequent intervals and the administration of alkalies and weak tea.

5. Recovery is usual. A ' follow-up ' of children after their discharge from hospital showed that recovery is complete, remissions rarely occur and the subsequent general health of the children is not impaired.

6. Urinary infection in the neonatal period occasionally occurs either as a complication of intracranial birth injury or in association with severe alimentary disturbance.

7. In fatal cases pathological changes are slight: they are most often found in the kidney substance and rarely involve the pelvis of the organ.

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BLOOD COUNTS OF NEWBORN INFANTS IN RELATION TO ICTERUS NEONATORUM

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This investigation into the blood picture of newborn infants was made primarily to determine if any relationship existed between the erythrocyte count and the occurrence of icterus neonatorum. At the same time, independent information was obtained on the average blood count of newborn infants and the erythrocyte counts and haemoglobin estimations of infants born by caesarean section and natural means were compared. Literature on blood counts in the newborn extends over the last forty years, during which period the use of different methods of investigation detracts considerably from the value of older findings, obtained when apparatus was relatively crude and when haematology was less exact than it is to-day. Information on the subject of icterus neonatorum is more satisfactory; the fundamental cause has recently been postulated and experimentally confirmed in animals, but the fact that it occurs in some infants, and not in others, is still not explained.

Icterus neonatorum is relatively common in newborn infants, the incidence according to various authorities varying between 30 per cent. and 80 per cent. It is said to be more frequent in small and premature infants and among the poorer classes. Jaundice usually appears on the second day after birth, and may persist as long as two or three weeks. Infants do not appear adversely affected by the jaundice, which is the only clinical finding.

Previous work.

The most recent and attractive theory of causation of icterus neonatorum has been put forward by Goldbloom and Gottlieb, who produced confirmatory experimental evidence in animals.

They argued[1] that the mixture of arterial and venous blood circulating in the human foetus was comparable to the blood of a human adult living in a state of diminished oxygen tension which had produced a polycythaemia. With the birth of the infant and cessation of diminished oxygen tension, the necessity for polycythaemia ended, a compensatory haemolysis of

redundant red blood cells occurred and icterus neonatorum ensued. In support of this theory the same investigators[5] kept guinea pigs under reduced oxygen tension, and were able to produce a polycythaemia with appearance of reticulated red cells in the circulation. On restoring the oxygen tension to normal the animals' erythrocyte counts returned to normal, but the icteric index of the serum was raised, and the van den Bergh reaction showed an indirect positive result. Thus conditions similar to icterus neonatorum were produced. The same workers later demonstrated[6] that while maternal blood showed normal oxygen saturation and capacity values, foetal arterial blood possessed a decreased oxygen saturation due to deficient respiratory function in utero. Barcroft[2], in a study of foetal respiration, mentioned that the blood was red in icterus neonatorum, partly from excess haemoglobin 'engendered by oxygen want' and partly from the foetal type of haemoglobin 'which acquires oxygen with ease, though it sheds it with difficulty.' Barcroft also stated that towards the end of foetal life much haemoglobin was broken down and the iron stored in the liver, to be used again post-natally. Andrewes[1], who studied the van den Bergh test in jaundice, found 'almost invariably a latent jaundice at birth,' as indicated by the icteric index of the serum, explainable by the breakdown of haemoglobin before birth mentioned above. In thirty-eight cases he found, however, only a rough correspondence between the degree of bilirubinaemia at birth and subsequent occurrence of icterus neonatorum. Cases with a high bilirubinaemia commonly developed jaundice, and cases with a low reading usually did not, 'yet it was impossible to foretell with certainty—from the amount of pigment—whether jaundice would appear or not.' Hirsch and Yllpo[7, 8] showed that the bilirubin content of the serum rose to a variable height during the first few days of life and then fell. They found that the peak, reached after a few days, determined the occurrence of icterus neonatorum, rather than the initial height at birth.

Bearing in mind these findings, and assuming that the source of bilirubin must be haemolysed erythrocytes, we followed the erythrocyte count of infants from birth for the first five days.

Material and methods.

Twenty infants, born at full term according to the menstrual and clinical evidence of the mothers, were investigated. Of these, ten were born by caesarean section and ten by natural means.

Method used for cell counts.—Blood was obtained approximately one to two hours after delivery, when the infants had been bathed and their peripheral circulation established, thus avoiding misleading results from stagnation of blood in the extremities. Blood was obtained from the heel by a stab with a triangular needle deep enough to ensure a steady flow without any squeezing or pressure.

RED CELL AND WHITE CELL COUNTS were made separately in a counting chamber having the improved Neubaer ruling, an average of two consecutive counts being made in each case.

DIFFERENTIAL WHITE CELL COUNTS were made on films stained by Leishman's stain, 200 cells being counted.

HAEMOGLOBIN ESTIMATIONS were made by Haldane's method.

After birth red cell counts were made as far as possible at twenty-four hourly intervals.

Results.

Of the series of twenty infants, nine developed icterus neonatorum, a percentage of 45. Seven infants developed jaundice on the second day, and two on the first day after birth. No co-relation between the birth weight and development of icterus was found.

(1) **At birth,** average erythrocyte counts and haemoglobin estimations for infants developing icterus neonatorum, and for those who did not, were as follows:—

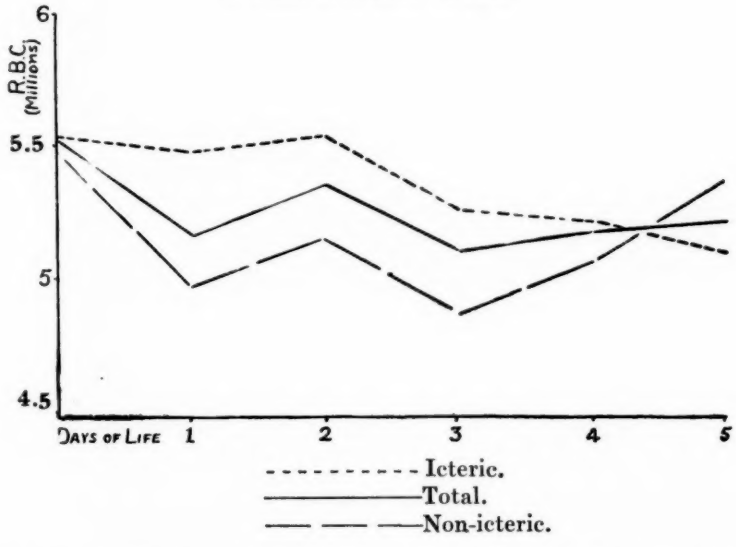
	Red cells per c.mm. (millions).			Haemoglobin.
	Average.	Maximum.	Minimum.	per cent.
Icteric	5·528	6·080	4·78	119
Non-icteric	5·499	6·875	4·67	117

These values are so close as to be within limits of technical error: hence it is concluded that no difference exists at birth in the erythrocyte count or haemoglobin value of the two classes. It is noteworthy that the maximum and minimum values in the two classes are comparable.

(2) **Subsequent daily erythrocyte counts** showed that infants developing icterus neonatorum had a higher average count than either the total average, or the average of those without icterus (see chart I). Similarly

CHART I.

Curves showing average of daily erythrocyte counts in first five days of life.



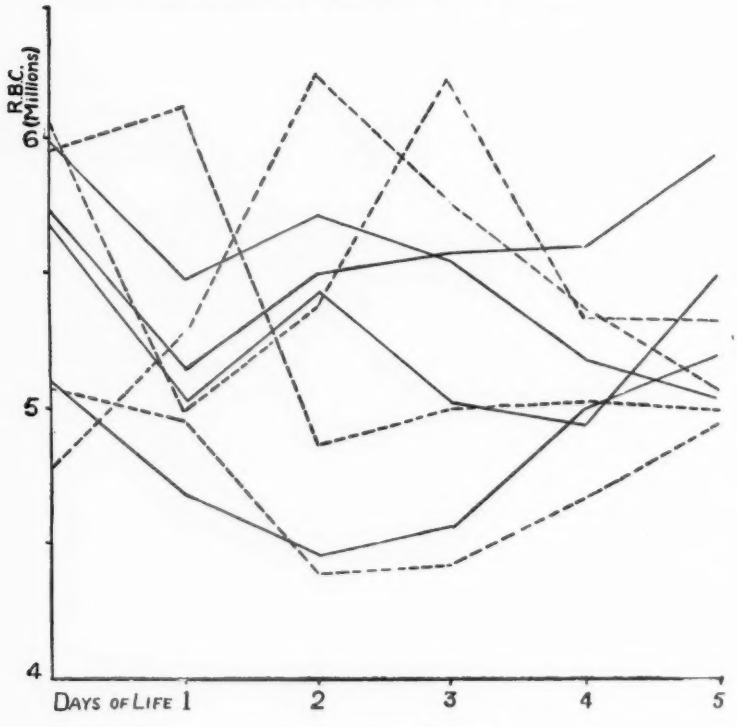
the non-icteric curve was lower than either the total average or icteric curves. All curves showed a downward tendency, and it is noteworthy that on the fifth day the average counts in both classes were within 250,000.

In individual daily curves a peak was reached on the second or third day in some infants developing icterus, followed by a fall. This fall in the erythrocyte count presumably corresponds to the rise in serum bilirubin described by Hirsch and Yllpo. However, the fact must be emphasized

that, given a curve of erythrocyte values in the first five days of life, it is impossible to deduce from it whether the infant had developed icterus neonatorum or not, as shown by the chart of individual values (see chart II).

CHART II.

SPECIMEN CURVES OF INDIVIDUAL INFANTS SHOWING ERYTHROCYTE COUNTS DURING FIRST FIVE DAYS OF LIFE.



	TOTAL RED CELLS (MILLIONS).	ICTERIC.	NON-ICTERIC.
Birth	5·512	5·528	5·499
1st day	5·160	5·446	4·996
2nd ,,	5·367	5·548	5·160
3rd ,,	5·110	5·277	4·877
4th ,,	5·176	5·234	5·080
5th ,,	5·215	5·118	5·337

Average erythrocyte counts on first five days of life.

Discussion.

Andrewes concluded regarding bilirubin, the derivative of erythrocytes, that it was impossible to foretell from the amount of pigment whether jaundice would appear or not. It was similarly concluded from the present study of the erythrocytes themselves that it is impossible to predict from the erythrocyte count at birth whether an infant will develop icterus neonatorum or not. Erythrocyte counts during the first five days of life showed a higher average curve in infants developing

icterus neonatorum and a slightly lower curve in infants not developing icterus, as compared with the average curve of all cases. But from individual infants' curves, nothing could be deduced. It is, therefore, believed that more than one factor exists in the production of icterus neonatorum, and it is submitted that the factors are:—(1) The degree of activity of erythrocyte production; and (2) the degree of activity of the reticulo-endothelial system, in short, a balance between erythrocyte production and destruction.

To maintain intra-uterine polycythaemia erythrocyte production must be active, as is borne out by the presence of nucleated red cells and polychromatophilic cells in smears from the newborn and after birth the production slows down to maintain a lower erythrocyte level.

Redundant erythrocytes are destroyed by the reticulo-endothelial system with consequent production of pre-hepatic bilirubin which, if produced in excess, causes jaundice. It is believed that this excess bilirubin production is an expression of reticulo-endothelial over-activity, either of itself or imposed upon it by over-production of erythrocytes.

In the present series of infants, those developing icterus neonatorum showed a higher average curve for erythrocytes during the first few days of life than the average of all cases, pointing to a persistence of intra-uterine activity which only died down gradually, and compensatory reticulo-endothelial activity.

In view of the radical change from intra-uterine to extra-uterine conditions, it is not surprising that these systems overshoot the mark, one way or the other, before attaining physiological balance.

The apparent paradoxes of a low erythrocyte curve with icterus neonatorum, and a high erythrocyte curve without, are thus explained:—

		Erythrocyte production.		R-E. activity.
Icterus with low curve	=	Normal or under-active	+	Over-active
Icterus with high curve	=	Over-active	+	Over-active
No icterus with low curve	=	Normal or under-active	+	Normal
No icterus with high curve	=	Over-active or normal	+	Under-active

The fact that icterus neonatorum only occurs in some infants despite an initial polycythaemia in all, can thus be also explained. The transient nature of the jaundice, and the close proximity of average erythrocyte counts on the fifth day of life in both icteric and non-icteric infants, lends colour to the submission that icterus neonatorum is the result of trial and error between two physiological processes before they attain harmony.

Cell counts at birth.

Both the erythrocyte and white cell counts in an adult offer many possible sources of error, both technical and personal, in their estimation,

but in a newborn infant is superadded both variation in the quality of blood from different sources (Drucker[3]), and a variable stagnation of peripheral blood due to birth trauma and the radical change in the respiratory and circulatory systems at birth. Each investigator, setting his own standards can attain considerable accuracy in counts, but the comparison of different workers' results is impossible without the use of standard methods. For these reasons it is only possible to refer to an 'average' cell count at birth, as opposed to a 'normal' count at birth (see table below).

ERYTHROCYTE VALUES AT BIRTH.

	Year.	Erythrocytes per c.mm.	
Aitkin[9]	1902	6,130,000	
Fehrson[10]	1904	6,047,000	Haemoglobin average 110 per cent.
Lucas et al[14]	1921	5,511,000	Haemoglobin average 117 per cent.
Mayers[16]	1922	7,630,000	
Lippman[13]	1924	5,200,000	
Zibordi[19]	1925	6,380,000	Haemoglobin average 114 per cent.
Forkner[11]	1929	5,963,000	Haemoglobin average 148·5 per cent.
Hawkesley & Lightwood[12]	1934	5,500,000 6,000,000	
Whitby & Hynes[17]	1935	7,000,000	Haemoglobin average 151 per cent.

Mackay[15] tabulates the findings of, Appleton (1918), Hallez (1919), Hutchison (1904), Schiff (1890), and Williamson (1916). All investigators are agreed on a polycythaemia. In the present series of twenty cases the erythrocyte count at birth was found to be:—

	Average.	Maximum.	Minimum.
Red cells per c.mm.	5,512,000	6,875,000	4,670,000
Haemoglobin, per cent.	118	140	102

The white cell and differential counts were made in fourteen of the cases, with the following results:—

		Average.	Maximum.	Minimum.
Total white cells per c.mm.		13,350	19,500	10,200
Neutrophil polymorphs	per cent. of W.B.C.	59·8	82	38·5
Eosinophil polymorphs		2·1	4·5	0
Lymphocytes		35·6	53·5	2·0
Large mononuclears		2·5	6·0	0
Normoblasts		3·5	14	0

Caesarean section.—Ten of the infants in the series were delivered by caesarean section at full term, for the following maternal reasons:—recent myomectomy 2; disproportion 6; myocardial degeneration 1; and ankylosis of left hip 1. The average red cell and haemoglobin values for ten caesarean-born infants are slightly, but definitely, lower than those of ten

children born by natural means. This is probably due to the elimination of cyanosis and trauma associated with passage through the birth canal.

	Caesarean. Average.	Caesarean. Maximum.	Caesarean. Minimum.	Natural birth. Average.
Red blood cells, millions per c.mm.	5·381	6·080	4·670	5·633
Haemoglobin per cent.	114	125	108	121

Of the ten caesarean-born children, three developed icterus neonatorum —30 per cent. Of ten naturally-born children, six developed icterus neonatorum—60 per cent. These figures are not discussed because of the small number of cases.

Conclusions.

(1) The erythrocyte count at birth bears no relationship to development of icterus neonatorum.

(2) The average five-day erythrocyte curve of icteric infants is higher, and that of non-icteric infants lower than the average curve of all cases.

(3) No conclusion can be drawn from an individual five-day curve as to the occurrence of icterus neonatorum.

(4) Icterus neonatorum is an expression of temporary lack of balance between erythrocyte production and destruction.

(5) Average values are given for cell counts and haemoglobin estimations of newborn infants.

(6) Caesarean-born infants show a slightly lower average erythrocyte count and haemoglobin estimation than naturally-born infants.

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RECURRENT SWELLING OF THE PAROTID GLANDS

BY

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In the following paper a series of cases is described of recurrent swelling of the parotid gland of a type which hitherto has not been clearly recognized. Recurrent swelling, the result of infections of the gland or its ducts is well known as in the cases reported by Payne[7] and Pyrah[8, 9]. In the eleven cases now to be described infection seems to play but a small part in the etiology of the condition, which differs in several features from the recurrent pyogenic parotitis of Payne.

Clinical records.

The main features of the cases, summarized in table I, are as follows:—

The majority are children, seven of the series being under twelve years of age, eight are males and four females. The onset usually occurs without obvious predisposing causes. The swelling affects one or both parotid glands: it may be bilateral from the start, may affect one side before the other or remain unilateral, and always appears to involve the entire gland. It varies in size, not only in different individuals but in the same patient in different attacks, from a slight fullness of the face to a swelling sufficiently prominent for a mistaken diagnosis of mumps to be made. It may occur daily over a long period or recur at intervals of months or years, and may last for only a half an hour or persist for several days. The swelling develops quickly and the onset not infrequently coincides with the taking of food. Acid foods in particular are often mentioned as precipitating factors. In two patients (no. 5 and 8) the consumption of certain definite foods was thought to be associated with attacks but in the remainder there was no apparent connection with specific articles of diet, and the association of swelling with eating seems merely to depend on the increased secretory activity accompanying mastication. In this respect the history resembles that of stone in Stenson's duct, which must always be excluded.

The development of the swelling is usually accompanied by a feeling of tension and this may give rise to actual pain. In many cases, however, pain and local tenderness are absent, and pressure can be applied over the swollen gland without evoking signs of distress. It is uniformly firm and smooth to the touch and the skin over it is neither reddened nor hot. The

Case	Age in years and sex	Duration of symptoms in years	Unilateral or bilateral	Frequency	Precipitating factors	Infection preceding first attack	Parotid secretion
							NON-INFECTED
F. E. 1	8½ M.	7	Bilateral	2-3 annually Recently every month	Colds sometimes	None	Clear saliva containing occasional epithelial cells during attacks
F. C. 2	4½ M.	3/12	Bilateral	Monthly	Acid food or fruit	None	Clear during attacks: not microscoped
M. C. 3	26 F.	19	Bilateral	Daily now occasionally	None	None	Not seen during attack, clear in interval
C. P. 4	5½ M.	3½	Bilateral	Every 3 wks. in summer. Occasionally in winter	None	None	Clear during attack: not microscoped
M. P. 5	52 F.	8	Bilateral	Severe every 4 weeks. Slight in winter	Taking food especially fish and acids	None	Clear saliva containing plugs packed with eosinophils during attacks
P. P. 6	7	3	Bilateral	3 or 4 a year. Formerly more frequent	None	With pneumonia	Clear during an attack. Dry mouth
D. L. 7	6½ M.	1/12	Bilateral	2 attacks	None	None	No secretion seen, mouth dry
J. M. 8	26 M.	6	Left	Monthly, more often in summer	None	None	Clear fluid while swelling is present. Not microscoped.
L. H. 9	9 M.	5	Left	2 swellings only	None	None	Clear during attacks. In interval a few epithelial cells
M. H. 10	25 F.	3	Right	3 swellings	None	None	Clear and scanty during attack. Not microscoped
J. F. 11	8 M.	2/12	Right	1 attack 2/12 ago, for last 3 wks. daily	None	None	Clear during attacks. No cells
							INFECTED
N.K. 12	10 F.	6	Bilateral	1 or 2 annually	Acid foods	Measles	Pus and debris and strept. Purulent during attacks. Clear during interval
L.L. 13	8 M.	8/12	Bilateral	5 attacks	Sore throats	Scarlet fever	Mouth dry and no secretion seen
J.P. 14	6 M.	4½	Bilateral	Recently daily, formerly only on occasions	Food	None	Turbid during attack. Pus and epithelial cells
F.S. 15	11 M.	2	Bilateral	Every fortnight	Cold temperature	None	Pus and debris. Epithelial cells
B.H. 16	3½ F.	3/12	Left	Daily variations	Worse on waking	None	Clear. Epithelial and occasional pus cells seen under microscope
S.B. 17	7½ M.	2	Left	Irregular from 2 wks. to 6/12	None	Followed otitis media on same side	Purulent during attack. Clear in interval

State of orifice of duct	Signs of infection	Allergy		Sialogram	Remarks
		Personal	Family		
CASES.					
Normal	None	None	None	Dilatation of terminal ducts	Injection of lipiodol caused immediate swelling of glands which remained swollen for some hours
Normal	None	Rhinorrhoea	Grandfather asthma	Dilatation of terminal ducts	Eosinophilia 10 per cent. Swelling of left side preceded that of right by some mths
Normal	None	None	None	Dilatation of terminal ducts	Sister of Case-J.P. Not observed during attacks.
Normal	None	Pap. urticaria	Grandfather asthma	Dilatation of terminal ducts	Pap. urt. in summer only and is then often coincident with parotid swelling. 9 per cent. eosinophilia
Patulous	None	Asthma angioneurotic oedema, hay fever	Brother eczema. Cousins hay fever	Gross dilatation of main and branch ducts	The severe attacks coincide with the severe attacks of asthma. Sialogram see figure 1, d
Normal	None	Asthma	None	Dilatation of terminal ducts. Bilateral	Pyrexial with attacks—mouth dry in attacks—swelling lasts 3 days; one side usually precedes the other
Normal	None	None	Mother migraine	Normal	Tonsils removed 3 mths. before first attack. Mouth dry and pyrexial when seen in attack
Normal	None	Asthma, hay fever, abdominal colic	Mother eczema. Uncles rhinorrhoea	Normal (L).	Swellings are often associated with colic and are then more severe. Sialogram see figure 1, a
Normal	None	Asthma, eczema	Grandmother asthma ? ? Mother eczema	Normal (L).	
Normal	None	Hay fever, urticaria	None	Normal (R).	Attacks accompanied by malaise, usually start during a meal
Normal	None	Pap. urticaria	Grandmother asthma. Mother hay fever	Dilatation of terminal ducts (R). Normal (L).	
CASES.					
Reddened duringattack	Not seen in attack	None	None	Dilatation of terminal and medium sized ducts. Bilateral	Swellings persist for a week. Child feels ill during swelling and is pyrexial. Right side only was affected for first 4 years
Reddened, patulous duringattack	Tender	Pap. urticaria, pork idiosynerasy	None	Normal	Pyrexial during attacks. Dry mouth and cracked lips. Attacks last a week and associated with sore throat. 9 per cent. eosinophilia
Normal	Slight heat and tenderness over glands	None	None	Dilatation of terminal ducts. Bilateral	Glands palpable between attacks. Brother of Case 3. 5 per cent. eosinophilia. Sialogram, see figure 1, c
Reddened duringattack	Local heat and tenderness	None	Brother asthma	Dilatation of terminal ducts. Bilateral	Attacks often associated with colds
Normal	None	Pap. urticaria	Grandmother eczema	Dilatation of terminal ducts. Bilateral	Swelling persisted with fluctuations for 6 weeks in first attack
Normal	Redness and tenderness reported by mother	Pap. urticaria	Brother eczema possibly infective	Normal. (L).	Swellings usually last for several days. 7 per cent. eosinophilia

regional lymph glands are not enlarged and trismus is not present. The parotid gland itself cannot be palpated between the attacks. The condition of the mouth is healthy, and only two patients complained of dryness during attacks (no. 6 and 7). The openings of Stenson's ducts are not reddened: they are sometimes difficult to detect, as in some normal subjects, but they can always be rendered obvious by introducing lemon juice or an acid sweet into the mouth for a few moments. Clear saliva is seen to escape from the duct orifices in the majority when the swelling is present, and this may sometimes be increased by pressure over the affected gland. In other cases, however, no flow of saliva from the parotid duct was seen at the time of the swelling.

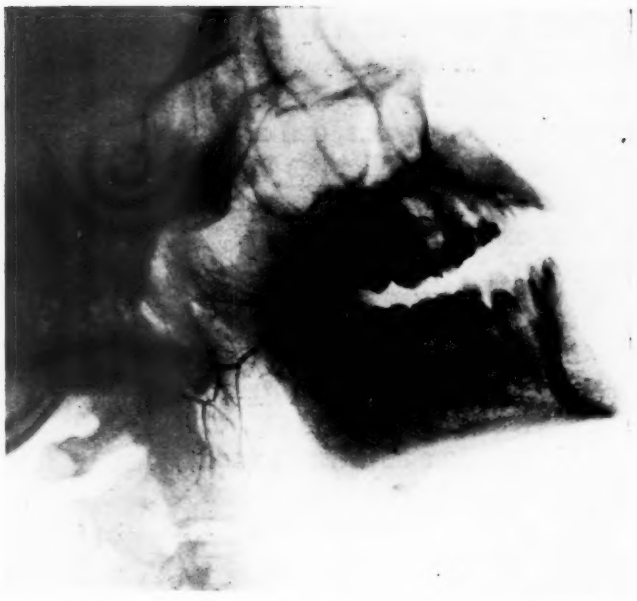
Sufficient observations have not yet been made to decide whether these variations depend on the stage at which the swelling was observed, that is during its development, at its height or during subsidence, or whether the findings are constant in the same individuals on different occasions or not. Microscopical examination of the fluid obtained from the duct while the swelling was present was carried out in several instances and showed that the saliva was either quite clear or contained a few epithelial cells, and differed in no way from fluid obtained similarly between the periods of swelling. Case no. 5 is an exception and the findings in her case are described fully later. Mantoux tests (O.T. $\frac{1}{1000}$) were carried out in four of these cases and a positive result was obtained in one (no. 6).

In every case radiological examination of the parotid duct and its branches was carried out after the injection of lipiodol. A hypodermic syringe fitted with a blunt ended 20-gauge needle or a lachrymal duct cannula was employed. Lipiodol was injected until a feeling of tension was experienced in the region of the parotid gland: this generally occurred after 0·3–0·6 c.c. had been injected, but one patient (no. 5) retained over 3 c.c. At this point when more was injected, the lipiodol could be observed escaping from the duct along the side of the needle. On withdrawing the latter, escape of lipiodol was prevented by placing a finger inside the mouth over the opening of the duct, and exerting counter-pressure against it on the outside of the cheek with the thumb. The finger was removed from the mouth immediately before exposing the x-ray plate: in those patients in whom the swellings were bilateral both sides were examined in this way, usually on separate occasions, and bilateral examinations were also carried out in those cases of unilateral swelling in which the appearance on the affected side was thought to be abnormal. In cases of unilateral swelling in whom the x-ray appearance on the affected side appeared to be normal, the other side was not examined.

Of the eleven cases forming the group under discussion, bilateral swellings were present in seven. Five of these showed small dilatations of the terminal ducts or acini (see fig. 1). One (no. 5) showed gross dilatations of the main duct and its branches: the finer ducts either failed to fill or appeared normal (see fig. 1). In one case (no. 7) the appearance was regarded as normal. Of the remaining five cases, in which the swelling

SIALOGRAMS.

FIG. 1.



a. Case no. 8. Sialogram showing normal appearance.

b. Case no. 4. Sialogram showing dilatation of terminal ducts.

c. Case no. 14. Sialogram showing terminal dilations, and moderate dilatation of main and branch ducts.

d. Case no. 5. Sialogram showing gross dilatation of main and branch ducts.

was limited to one side, the terminal ducts were dilated in one (no. 11), while the appearance on the other side was normal: the other four cases showed no abnormality (see fig. 1). It is clear that apart from the fact that the appearance of the ducts is frequently abnormal, particularly in cases with bilateral swellings, no constant radiological features are shown.

In order to exclude the possibility of over-distension with lipiodol being responsible for the small terminal dilatations referred to, radiological examination of the salivary ducts was also carried out by the same method, in ten control cases between the age of five and twelve years, and one aged thirty years. In all these the findings corresponded with what has been regarded as normal by other authors, notably Pyrah and Allison who state that they too have investigated a number of controls.

A striking feature of these cases is the frequent association with conditions usually referred to as ' allergic.' Thus eight of the eleven patients in the series are or have previously been the subject of some allergic manifestation: asthma occurs in four cases (no. 5, 6, 8, and 9), papular urticaria* in two (no. 4 and 11), hay fever in three (no. 5, 8, and 10), while spasmodic rhinorrhoea (no. 2), angioneurotic oedema and urticaria (no. 5), and eczema (no. 9) are each present in one case. In one patient (no. 8) attacks of colic following the consumption of certain foods was thought to be due to sensitization. In five of these cases there was in addition a family history of allergy and this was also obtained in one other (no. 7) so that nine patients had a personal or family history of allergy. A raised eosinophil count in the blood was observed in several cases. In the majority there was no evidence of any relationship between the development of the swellings and the occurrence of the allergic manifestations, but in three cases, referred to later the two forms of attack frequently coincided.

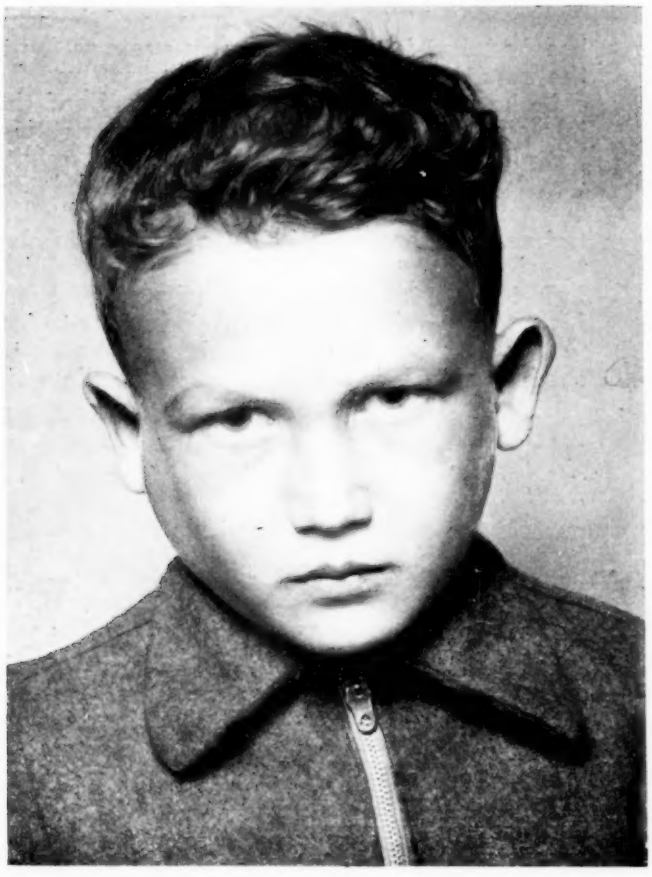
These are the main features of this group of cases, and the following case histories of individual patients serve to illustrate them more fully.

Case no. 1. F. E. was a boy aged eight-and-a-half years. There was nothing of interest in his family history and his health has been good except for an attack of measles. Since the age of one year he has had swellings in the region of the parotid glands on both sides: these occur once or twice a year. The swelling is sometimes limited to one side. It develops suddenly and may last for a day or more. Colds appear to predispose to attacks. On examination there was bilateral swelling of the parotid glands (see fig. 2), which were firm but not tender to the touch. There was no heat or reddening of the skin. The mouth was clean and clear saliva was seen to issue from the duct orifice, which appeared normal: microscopical examination of the saliva obtained from the duct at the time of the swelling, revealed the presence of a few epithelial cells but no other abnormality.

* Papular urticaria and migraine are for the purposes of this paper regarded as allergic states, though it is recognized that there are other factors probably of greater importance in their etiology.

One month later the mother reported that the swelling had occurred every morning for the past week subsiding again during the day. The week following, no swelling was apparent and bilateral radiological examination following injection of lipiodol into Stenson's ducts, revealed bilateral terminal dilatations. This procedure was followed within ten minutes by rapid swelling of both glands, which subsided within the next half hour but remained visible for two days. When seen five months later slight degrees of swelling had occurred several times, but had caused no inconvenience. The boy's general health was good.

FIG. 2.



F. E. Photograph illustrating appearance during moderate swelling of parotid glands.

The following three cases are those already referred to, in whom there was a clearly recognizable relationship between the parotid swellings and the associated allergic conditions.

Case no. 4. C. P. was aged five-and-a-half years. A grandfather suffered from asthma. The swelling was bilateral and of moderate size but was more pronounced on the right side than on the left. It began at the age of one year and ten months and

has recurred at intervals of about six weeks. During the summer it occurs more frequently and is then often associated with attacks of papular urticaria. The mouth was often dry during the attacks. Clear saliva was seen to escape from Stenson's duct, but none was obtained for microscopical examination. Sialography again showed bilateral terminal dilatations. Positive intradermal skin reactions to mutton and pork were obtained, but there was no clinical confirmation and no special significance was attached to them.

Case no. 3. J. M. was aged 26 years. His mother suffers from eczema, and several members of his father's family have spasmodic rhinorrhoea. He is an only son and lives on a farm. At the age of fifteen, he had eczema of the arms and axillae. He has had hay-fever in the early summer for ten years, and for the past three-and-a-half years has suffered from asthma. As a child he suffered from ' bilious attacks ' and these have continued into adult life. They may come on after eating pork or dripping, but also occur without any recognized precipitating factor. The attacks begin with colicky pain in the left iliac fossa, and lead to vomiting and sometimes diarrhoea, with the passage of much mucus. At the same time the left parotid gland swells and may remain up for two or three days. The swellings also occur apart from these attacks, and are particularly frequent during the hay-fever season. He gives no skin reactions to foods, but gives large reactions to horse dander, and smaller ones to chicken feathers, cat hair, dog hair dust extracts and pollens (intradermally).

Examination of this patient was possible on one occasion only. At this time there was slight swelling in the region of the left parotid gland. The orifice of Stenson's duct was normal and clear saliva was seen to pass into the mouth. The x-ray appearance of the ducts was normal.

Case no. 5. M.P. was aged 52 years. A brother has eczema and several cousins hay-fever. The patient has had hay-fever for many years. The parotid swellings which are bilateral have occurred intermittently for eight years; she has had attacks of asthma for a slightly shorter period. The latter are usually accompanied by the swellings which become hard like cricket balls and are painful. During the time that these severe attacks are present, the pain is greatly increased if pressure is applied over the gland; after a few hours however a sensation of subjective improvement is experienced, and at this time pressure causes the expulsion of a stream of saliva into the mouth with further relief of symptoms. In between the major attacks, which occur at intervals of several weeks, minor degrees of swelling are frequently noticed, and mastication of food or even the thought of it may be sufficient to precipitate these. The patient has observed that eating fried fish is particularly apt to be followed by an attack of asthma, with swelling of the floor of the mouth and associated parotid swellings. Occasionally the tissues around the orbit become swollen in addition. This appears to be due to angioneurotic oedema rather than any swelling of the lachrymal glands. Recently she had noticed swelling on both sides in the floor of her mouth. These have not been seen but from her description would appear to be swellings of the sublingual glands.

When first examined there was a soft swelling of moderate size involving both parotids; the orifices of Stenson's ducts which were slightly patulous were clearly seen on opening the mouth, and this act caused the ejection of clear saliva. On several occasions pressure over the glands caused a plug of viscid material to be ejected, followed by a gush of several cubic centimetres of clear fluid.

Examination of the plugs showed that these were about three cm. in length and the thickness of a piece of string. When spread on a slide and examined microscopically, they were found to consist of a clear matrix closely packed with cells. These were almost entirely mature, perfectly formed, large granulated eosinophils. A count kindly carried out by Dr. F. H. Knott gave the following picture:—Eosinophils, 96 per cent.; polymorphs, none seen; endothelial cells, 2 per cent.; and small round cells, 2 per cent. Epithelial cells were seen in small numbers, but no organisms could be detected in a direct smear.

The parallel between these parotid plugs and the Kurschmann's spirals seen in asthmatic sputum seems to be close.

Discussion.

It is clear from what has been said that these cases differ from those previously described by Pyrah and Payne. In the first place their patients were considerably older; the average age at onset in Payne's nineteen cases of recurrent pyogenic parotitis is twenty-nine years, the earliest being eleven years, while Pyrah's four cases are between sixteen and forty-seven years of age. Secondly, the parotid swelling was accompanied in their cases by clear signs of inflammation, such as heat, redness and pain, reddening of the orifice of the duct, a foul taste in the mouth and the passage of purulent or turbid saliva. There was also induration of the gland which rendered it palpable in the intervals between periods of swelling. Moreover in these cases the condition almost invariably began unilaterally and later spread to involve the opposite side. In five of the present series of cases the condition was bilateral from the beginning. Lastly, neither Pyrah nor Payne report association of the parotid swellings with allergic conditions though they do not state if this association was sought for.

It therefore seems justifiable to seek some explanation other than infection for the origin of the recurrent swelling in the present cases. From this point of view the frequent association with allergic conditions in the personal and family history is of special interest. This frequently is so high as to point to more than a chance relationship. In addition the intimate associations between the occurrence of the swellings and other allergic phenomena in three of the cases make it reasonable to suggest that the recurrent swellings of the parotids may themselves be an allergic manifestation while the presence of eosinophil-containing plugs in the parotid secretion makes this likelihood still greater in one case.

The conception of allergy as an explanation for parotid swellings is not new. Vogeller[13] in 1922 described a case of recurrent parotid swelling

occurring in a woman of forty-three. When this began seven years before, it was sudden in onset and painless: relief was obtained by expressing a white plug from the duct. Later the swelling became associated with fever and pain, and enlargement of neighbouring lymph glands. A blood count showed an eosinophilia of 11 per cent. He comments that the original incidence of swelling indicates some obstruction: the plug when removed was not followed by copious secretion or immediate subsidence of the swelling. Obstruction, therefore, does not entirely explain the condition. He believes that the swelling of the gland occurs as a result of a process similar to angioneurotic oedema of the subcutaneous tissues. He also suggests that later, secondary infection from the mouth has occurred leading to destruction of the glandular tissue with sialodochitis. The condition is likened by him to asthma. Burton Fanning[1] in 1925 described a case of recurrent parotid swelling in a man aged sixty-two years associated with a dry mouth and attacks of rhinorrhoea; on one occasion an injection of adrenaline cut short an attack. More recently Meyer[5] has described under the title of ' chronic sialodochitis ' the case of a child of six years in whom parotid swellings were associated with passage of ropy saliva. The swelling was usually unilateral but affected opposite sides in different attacks. There were no signs of inflammation but various organisms were grown from cultures of the parotid saliva; it is difficult to be sure that these were obtained under strictly aseptic conditions. Positive skin tests to spinach, bacon and paprika were obtained, and removal of these from the diet together with chocolate, which was suspected on clinical grounds, was followed by freedom from the swellings for the following six months. While under observation, sialography showed dilatations of the minor ducts. The mother and great grandmother of this patient suffered from similar swellings. Although it has not been possible to find other records in which the authors have specifically cited allergy as a possible cause, several cases are recorded in which it seems possible that the condition was allergic in origin. One of the most interesting is the case described by Kussmaul[3] in 1879, and referred to by him as a case of ' fibrinous sialodochitis,' a term he was the first to use. The patient was a woman of thirty-two years who had a four years' history of unilateral recurrent swelling of the parotid. Her only previous history was one of frequent pain in the jaw on that side following trauma as a result of removal of a tooth. The swellings were at first painless, and might last for a period of half-an-hour only, but later they became hot and painful and drops of pus exuded from Stenson's duct, as though infection had been superadded. The swelling subsided with expulsion of what is called a ' fibrinous plug.' This was packed with ' masses of round cells ' which resembled ' fresh pus cells.' Larger epithelial cells were present in smaller quantities and the presence of a Charcot-Leyden crystal was also noted. The extrusion of this plug was followed by a gush of clear saliva. Kussmaul argues that the gland itself was clearly not infected and regards the condition as similar to a chronic fibrinous bronchitis. This case resembles in many ways the cases of Vogeller and Meyer and of M. P. (no. 11) in our series. It would appear that as in Vogeller's case, infection was superadded after the condition had become established. It may well be wondered whether many of the cells seen in the plugs of this case were not in fact eosinophils—the use of the word ' fresh ' (frisch) applied to pus cells, the presence of a Charcot-Leyden crystal, and the fact that Ehrlich's method of differential staining was not then in use make it likely. Ipscher[2] in the same year records a similar condition affecting the submaxillary duct. Von Reuss[10] describes a patient, of sixteen years in whom parotid swellings occurred during the monthly period and in whom there was an eosinophilia, and in addition a girl of eight in whom parotid swellings were associated with abdominal colic. Londe and Pelz[4] also describe the

case of a child in whom the appearance of unilateral parotid swelling, and attacks of abdominal colic were common features though they are not described as occurring coincidently.

Even among cases presenting signs of infection, an association with allergy is not uncommon. In addition to the eleven cases described, six others have been observed in whom there was evidence of infection (see table). In four of these, pus cells were found in the parotid secretion which was clearly purulent in three (no. 12, 15 and 17), turbid in one (no. 14), and apparently clear in the fourth (no. 16). In the fifth case (no. 13) swelling always coincided with tonsillitis and the lips were dry and cracked: these attacks lasted for a week at a time and the patient was pyrexial during this time. No saliva could be obtained from the parotid duct during the presence of the swelling. In the last case (no. 12) there was a close but not invariable association with exacerbations of otitis media. Other signs of infection such as reddening of the duct orifice and heat and tenderness in the neighbourhood of the parotid gland were noticed in some of these cases.

Three of these infected cases (no. 14, 16 and 17) suffered from papular urticaria, one of them having in addition an idiosyncrasy to pork which was said invariably to cause vomiting. Two of these patients and one other gave a family history of allergy (no. 15, 16 and 17). The following cases show further points of special interest in this connection, and suggest that factors other than infection play a part.

Case no. 15. F. S., gave a history of swellings which were of two quite distinct kinds, namely those which persist for several days, were painful and tender and associated with an unpleasant taste in the mouth, and those which lasted for periods as short as twenty minutes and were not accompanied by any of these signs. Exposure to cold appeared to precipitate the short attacks: this factor is mentioned by Osler and Macrae[6] in their brief reference to acute swellings of the parotid gland. The saliva obtained from the left parotid duct during one of the severe periods was found to contain numerous pus cells, streptococci and clumps of eosinophils. A further specimen obtained three days after one of the short attacks contained a very few epithelial cells only. It is thought that the presence of eosinophils in the saliva, and the history of the brief periods of swelling, taken in conjunction with the presence of asthma in a younger brother offer strong support for the belief that infection has been superimposed on an allergic basis.

In the following patient there is also evidence that infection may not be entirely responsible for his condition:—

Case no. 14. J. P., has had swellings for over a period of four years. These have altered in character recently, having become more painful, and tender, and lasting for longer periods so that some degree of swelling is almost constantly present. The saliva was clear when the patient was first seen, but on one later occasion was turbid and contained pus cells. A blood picture showed the presence of 5 per cent. eosinophils. Moreover his sister, now a married woman of twenty-six years (no. 3) has suffered from a similar condition since childhood. The swellings have been slight

and infrequent for some years in her case, and she presents no signs of infection. A familial factor is thought to be present. It will be recalled that in Meyer's case a family history was also obtained.

Sialographic examination of these patients gives findings similar to those of the uninfected group, except that in two cases (no. 12 and 14) in addition to the terminal dilatations, there is some dilatation of the main and branch ducts. It is suggested that this is due to the infective process. It is also of interest with regard to patient no. 16, that although the swelling of which she complained was limited to the left side, terminal dilatations were revealed on both sides. In another case, in whom there was a unilateral parotid swelling associated with signs of inflammation and secretion of pus from the duct, bilateral dilatations were also observed.* This may well indicate a pre-existing bilateral condition of obstruction of the smaller ducts, on which infection has supervened on one side.

It is clear that radiography is of no value in determining the presence or absence of infection, since similar appearances are obtained in each group.

It seems probable that infection in at any rate some of these cases, occurs secondarily, and may well be superimposed on a condition of an allergic origin. This sequence of events has not been excluded in the cases of Pyrah and Payne, and may have been present in some of them.

Consideration of recorded cases, together with the observations carried out on the series, discussed in this paper, afford strong support for the belief that there exists a group of patients in whom recurrent swelling of the parotid gland is of allergic origin. At present this conception must remain a suggestion only, since as yet there is little understanding of the conditions called allergic, nor is there clear evidence as to the mechanism of the parotid swellings. It is also recognized that other causes of recurrent swelling undoubtedly occur. Apart from those cases in whom infection appears to be responsible, others are recorded in whom neither infection nor allergy seems to play a part. Such a case is that reported by Wolff[12] of an infant with enterospasm in whom manipulation of the stomach and intestines was associated with the sudden development of swellings: the author's suggestion of reflex spasm offers the most reasonable explanation. Von Steinitz[11] also records a case in which he believes increased viscidity of saliva may be responsible for the development of the swelling. Nevertheless, it is believed that, cases belonging to the present group are by no means uncommon. The frequent association of allergy in the patients and their relatives, the apparent absence of infection, the coincidence of the attacks of swelling with the associated allergic phenomena in three cases, and the presence of eosinophil-containing plugs in one of them are the chief grounds upon which the association with allergy is believed to be important. The

* This case is not included in the present series because the swelling had occurred on one occasion only.

frequent bilateral onset of the condition, the rapid development of the swelling, the presence of two cases in one family, and evidence that, even in six cases with infection, other factors were also present, are minor points of similar significance.

A number of possible factors come into mind as the immediate cause for recurrent parotid swellings. The enlargement may occur as a result of recurrent infections of the gland tissue itself, of the lymphoid tissue within it, or as a result of angioneurotic oedema. There may be obstruction of the duct by spasm, oedema of the lining membrane, or the presence of abnormally viscid saliva, mucous plugs, plugs of pus and epithelial debris or stone. Achalasia of the duct must be considered. If spasm occurs it may be due to the direct effect of some locally-formed substance on the muscle fibres, or as a result of a reflex mechanism. In the group of eleven cases described in this paper, there is reason to believe that infection plays no part. If this is excluded, the remaining mechanisms, with the exception of achalasia and stone, for neither of which is there any evidence, might all occur as the result of allergic processes. It seems probable that obstruction to the escape of saliva in the course of the parotid ducts is in most cases the immediate cause of the swelling. The tendency for it to develop during meal times, and the frequent presence of dilatation in some part of the course of the ducts, as shown by x-ray examinations after injection of opaque material support this contention.

Summary and conclusion.

(1) Eleven cases of recurrent swelling of the parotid gland are described, these are characterized by the absence of evidence of infection, and the frequent history of allergy.

(2) In three of the patients allergic manifestations frequently coincided with the development of the swellings. In one of these the passage of plugs containing large numbers of eosinophils from the parotid duct is described.

(3) It is suggested that these swellings may be allergic in nature.

(4) The possible mechanism of the swellings is discussed and obstruction of the ducts is thought to play a prominent part.

(5) Five cases in whom there is evidence of infection are also described.

(6) It is suggested that infection may in some cases be superimposed on an allergic basis.

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A FURTHER STUDY OF THE ANTIRACHITIC FACTOR IN HUMAN MILK

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Rickets is a common and important complaint in Egypt. The statistics published by Shawki[1] show that 50 per cent. of the Egyptian children between the ages of six months and two years have definite clinical manifestations of rickets. Such a high incidence of this disease in a country noted for its clear sky and abundant sunlight is naturally astonishing and the probable etiological factors concerned in the prevalence of this disorder among Egyptian children have been the object of many investigations in the last few years.

In 1932, Sabri and Fikri[2] experimenting with fat obtained from human, cow's and buffalo's milks (the milks commonly used for infant feeding in Egypt) came to the conclusion that these milks do not contain fully-formed vitamin D in amounts of any practical value in the prevention of rickets. On the other hand, they were able to demonstrate that these milks contain sufficient amounts of the precursor of vitamin D (provitamin D) which after activation by exposure to ultraviolet rays endows these milks with definite antirachitic powers.

The conclusion from the above experiments would be, that the infant, whether naturally or artificially fed, receives most of the antirachitic factor in its milk supply in an inactive form. Unless this factor is activated by exposure of the child to ultraviolet irradiation—obtained from natural or artificial sources—no protection against rickets is provided.

In 1933, Sabri[3] demonstrated that the amount of ultraviolet radiation in the sunlight of Egypt during the winter and spring seasons is far below that expected from the amount of sunshine. This is due to certain physical and meteorological circumstances. The abundant ultraviolet rays of the summer season are not of great benefit, as the excessive heat interferes with any sufficient exposure of the children to sunlight.

Thus, it is probable that the Egyptian child is not receiving as much ultraviolet radiation as would otherwise be expected. This, undoubtedly, plays an important rôle in the high incidence of rickets in Egypt.

Present investigations

The fact that more than 80 per cent. of the Egyptian infants are purely breast fed and that artificial feeding hardly exists in Egypt[1], facilitates the study of the rôle played by diet in the etiology of rickets in this country. The results of the experiments carried out previously on the vitamin and provitamin D content of the various milks used in Egypt in infant feeding have already been referred to. Our aim in the present experiments has been to find out any difference in provitamin D content of the milk of mothers living under the same conditions and nursing rachitic and non-rachitic children.

For this purpose milk was obtained from a group of two hundred healthy mothers attending the out-patient department of Foad I Children's Hospital and feeding healthy non-rachitic infants of an average age of six to twelve months and from another similar group of women nursing definitely rachitic infants of the same age as the former group. In both groups, the infants were exclusively breast fed and were not, nor had been, suffering from any general disturbance of any note. The mothers chosen were of the poor, working class coming from the same district of Cairo (Zeinhom) and living under practically the same conditions as regards housing and probably also diet. The percentage of fat in the pooled milk obtained from each group was estimated. The butter was extracted and heated in hot water baths at 40° C. until it changed to an oily consistency and all the remains of milk together with whey gravitated to the bottom of the container. The fat obtained in this way was exposed to ultraviolet radiation under standard conditions and mixed with the Steinbock and Black rachitogenic diet (No. 2965) in increasing percentages. The idea of using milk fat has been to avoid as far as possible the fallacies that arise from experimenting with whole milk (salt factor) on rats[2]. Albino rats of an average age of from four weeks and 40 grammes in weight were fed on the above rachitogenic diet plus the irradiated fat for a period of four weeks, being kept all the time in total darkness. At the end of that period, the left knee-joints were x-rayed, the animals sacrificed and the phosphorus of the pooled blood of each group was estimated. Throughout the experiment, the rats were weighed regularly. Any rats that did not gain weight properly were discarded.

In reading the skiagrams, the distance between the epiphysis and the diaphysis was measured in millimetres; a distance of less than 1 mm. was considered as slight rickets, between 1 and 2 mm. as moderate, and above 2 mm. as marked rickets. The results obtained are shown in the following table:—

Rats.	Diet.	X-rays.	Blood P. mgm. per cent.
Group A	Rachitogenic diet only		
1		marked rickets	
2		,, ,,	
3		— —	
4		,, ,,	
5		,, ,,	2·0
6		— —	
7		,, ,,	
8		,, ,,	

Rats.	Diet.		X-ray.	Blood P. mgm. per cent.
Group B	Rachitogenic diet + vit. D			
1	(vigantol)		no rickets	5·1
2			,, ,,	
3			,, ,,	
4			,, ,,	
Group C	Rachitogenic diet + 2 per cent.	of mothers nursing non-rachitic infants.		
1	irradiated milk fat		slight rickets	3·5
2			,, ,,	
3			moderate rickets	
4			slight rickets	
Group D	Rachitogenic diet + 4 per cent.			
1	irradiated milk fat		no rickets	4·2
2			,, ,,	
3			slight rickets	
4			no rickets	
Group E	Rachitogenic diet + 6 per cent.			
1	irradiated milk fat		no rickets	4·6
2			,, ,,	
3			,, ,,	
4			,, ,,	
Group F	Rachitogenic diet + 8 per cent.			
1	irradiated milk fat		no rickets	4·8 average P. = 4·3
2			,, ,,	
3			,, ,,	
4			,, ,,	
Group G	Rachitogenic diet + 2 per cent.	of mothers nursing rachitic infants.		
1	irradiated milk fat		moderate rickets	2·3
2			marked rickets	
3			,, ,,	
4			moderate rickets	
Group H	Rachitogenic diet + 4 per cent.			
1	irradiated milk fat		moderate rickets	2·7
2			,, ,,	
3			marked rickets	
4			moderate rickets	
Group I	Rachitogenic diet + 6 per cent.			
1	irradiated milk fat		slight rickets	3·4
2			moderate rickets	
3			slight rickets	
4			,, ,,	
Group J	Rachitogenic diet + 8 per cent.			
1	irradiated milk fat		no rickets	4·5 average P. = 3·2
2			,, ,,	
3			slight rickets	
4			no rickets	

It is evident from the above experiment that the content of provitamin D in human milk fat is definitely inferior in the milk fat of mothers nursing rachitic children to that of mothers feeding healthy non-rachitic ones. Estimates of the percentages of fat in the pooled milk

obtained from the two groups of mothers did not show any material difference.

Comment

Similar results were obtained by us in 1932[2]. The material then available, however, was small and the value of the results was limited. In the present experiments, on the other hand, more material was used and greater care was taken in the choice of cases. It should be noted, however, that the difference between the milk obtained from the two groups of mothers was not in the amount of fat but in the content of provitamin D present. The reason for the difference is not clear and the question requires further investigation.

The conclusions from the above experiments make it probable that the rachitic Egyptian infants, in addition to the deficient supply of ultraviolet rays, receive insufficient amounts of provitamin D in their milk supply. The amount of ultraviolet radiation in Egyptian sunlight seems to be just sufficient to prevent rickets provided that the child receives at the same time a generous supply of provitamin D. If the latter is also defective, rickets develops.

We wish to express our thanks to Dr. S. A. Naga, Radiologist, and Dr. M. A. Abboud, Resident of Foad I Children's Hospital for their great help.

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AN ENQUIRY INTO THE VALUE OF AUTOHAEMOTHERAPY IN JUVENILE ASTHMA

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In view of the uncertainty of the usual results of specific desensitization methods in allergic types of bronchial asthma, this enquiry was undertaken to determine whether the claims made in some quarters for the value of a course of injections of the patient's own blood in the relief of this distressing malady were justified or not. The reactions of the skin to foreign proteins of all classes of antigens, particularly pollens, dusts, foods, bacteria, orris root, etc., have been used in the past. Desensitization seriatim or by a mixture of the apparently offending substances has usually proved fruitless in our department. The skin sensitivity to the scratch method has varied greatly in the same individual tested at intervals. It appears to be a practical impossibility in hospital practice to test each child for every possible antigen to which he is exposed. The method of autohaemotherapy seemed a simple and easily-applied type of parenteral injection therapy which on grounds of economy should appeal to the most conscientious hospital board.

The series of asthmatic patients reported as treated by this method is small. The procedure is by no means new, as Kahn and Emsheimer[1] in 1916 obtained good results in six successive patients; Henske[2] subsequently was satisfied with the improvement in nine of sixteen patients and Carranza and Orgaz[3] reported ten out of thirteen patients to be ' much improved.' Achard and Flandin[4] used 0·5–2 c.c. doses every 12–24 hours, with better results in other allergic disorders than in asthma.

Present investigation.

Twenty-four patients (sixteen boys, eight girls) were selected for trial by this method. Before any injections were given the history of each child's illness was examined in detail and, unless this was thoroughly characteristic of an allergic form of bronchial asthma, the child was omitted from the series. A careful physical examination was supplemented by a otorhinologist's opinion upon the condition of the nose, throat and accessory nasal sinuses. An x-ray examination of the lungs and nasal sinuses and a fractional test-meal were carried out and finally the child's skin sensitivity was investigated

by the scratch method to the proteins of the ordinary foods, bedding materials, house dust, pollens, orris root, linseed and, frequently, to bacteria. If surgical attention was required for the nose or throat, this was usually provided before the first injection was made. Advice as to diet, elimination of allergens from the environment, and other forms of treatment or desensitization were deliberately withheld. Some children were taking dilute hydrochloric acid with their meals; this was suspended. All were supplied with a stock mixture containing ammonia, lobelia, iodide of potassium and senega for varying periods before the haemotherapy began.

Method.—A constant dosage of 10 c.c. of the child's own blood was withdrawn from the median basilic vein and injected forthwith into the buttock, without admixture with citrate and without any attempt to separate either plasma or serum. Five such transferences of blood were made in each patient at weekly intervals. A careful record was kept of the number and severity of the attacks during the course itself and for a period varying from three to twelve months afterwards. In assessing the results, the mother's description of the number and nature of the attacks was the only criterion. Similarly, a comparison between the description of the seizures before and after treatment could only be drawn from the parent's statements. Changes in the child's general appearance and body-weight were noted, since in almost all instances the patients were seen again at approximately monthly to three-monthly intervals, even if their malady had abated sufficiently to render less visits to the hospital necessary. Skin sensitivity was re-tested in instances in which ' great improvement ' was noted.

Results.—The difficulties of assessing the results of any treatment of asthma are notorious, especially when the series is small. Indeed, it is quite impossible to be at all dogmatic. The ever-changing allergic reaction in predisposed individuals provides the main stumbling block. No satisfactory measure of this state has yet been devised. Skin sensitivity is on the whole an unreliable index. Besides this quantitative variation in the intensity of the reaction as a whole, individual qualitative changes occur, whereby an allergic individual may alter the nature of his allergens during a period of medical observation such as that in the present series. In asthmatic children, who have usually a highly nervous make-up, the question of the psychological effect of these injections is uncertain. A conscious or unconscious determination not to require a repetition of the experience of sharp needles or Ryle's tube, may react favourably upon the severity of the disease in the post-injection period. As far as knowledge and experience is informative of other factors which may disturb the rhythm of the asthmatic state, a critical endeavour has been made to recognize conditions which could so vitiate the figures obtained. It has been observed that following the operation of tonsillectomy in childhood, there is often a relative or absolute remission from asthma, which may endure as long as twelve months. A change in address or other conditions of domestic environment has been enquired for. The presence of nasal or paranasal sepsis or of advanced

changes in the anatomy and pathology of the chest have meant either the elimination of a potential patient from the series, or if included, the results are assessed separately (class II). Furthermore, when a long interval has previously been admitted to exist between attacks, the patient has also been considered separately from the severer sufferers as follows:—

Class I. Patients in whom, as far as could be discovered, the injections have had a fair and unhindered opportunity of affecting the course of the disorder: 14 children.

Class II. Patients in whom other factors noted above have been present which may possibly have had an independent effect on the reading of the results: 10 children.

The results obtained in each class are described in terms of groups, as follows:—

Group I. No attacks of significance during at least six months.

Group II. Fewer and less severe attacks.

Group III. Attacks as frequent during period of observation, but less severe.

Group IV. No improvement noted.

	Group I	Group II	Group III	Group IV	Total
Class I	6	4	4	0	14
Class II	3	4	3	0	10
Total	9	8	7	0	24

Discussion.

The figures are too small to convert into percentages; but it is obvious at a glance that in each child treated something has occurred for the better, and it can be recorded that each patient, as will be seen from the protocols appended, is satisfied that the procedure has been to some degree at least beneficial. In nearly one half of those patients constituting group I a definite relief has followed. It is not to be expected, ab initio, that a procedure such as this is in any way of permanent benefit, but the palliative effect seems to last an average period of about six months. Cases 1, 2, 3 and 7 have been observed for twelve months, and in the first three of these the benefit has been maintained throughout this period.

Apart from psychological effects, it is interesting but difficult to conjecture the manner by which any benefit may accrue. There is no general reaction observable as with protein shock therapy. It is possible that tissue digestion of the blood protein releases peptone which is gradually absorbed as such. Very small amounts of Oriel's proteose may be present in minute desensitizing doses in the injected blood. It was intended to compare the results of the injection of separated washed corpuscles and plasma respectively, but this would require a further two years' observation, and more juvenile asthmatics than reach one medical out-patient clinic of a

general hospital. This small investigation was begun with an open mind. In assessing the results the authors have been deliberately critical concerning this application of the strange procedure of autohaemotherapy, which has given definitely favourable results. While the relief given may be quite temporary, by some means or other it gives the child a literal 'breathing space' during which it can develop physically and intellectually and so catch up with its more fortunate playmates.

Subsidiary investigations.

(a) Skin tests.—Effect of injections upon skin sensitivity: relation of our results thereto.

	Group I	Classes I and II Groups II, III and IV
Skin tests positive	9	6
Skin tests negative	2	6

The majority (fifteen out of twenty-four) of the patients demonstrated skin sensitivity to the common allergens. Nine (three-fifths) of these patients appeared to respond well to autohaemotherapy. Eight patients were negative to the scratch technique. Of these only two (one-quarter) responded as well as any of the nine children whose skins reacted as above.

(b) Age and heredity.—The influence of age, age of onset and heredity was also investigated, as follows:—

	Class I		Class II		Total
	Grp. I, II	Grp. III, IV	Grp. I, II	Grp. III, IV	
Under 10 years ...	6	3	1	0	10
10 years and over	3	3	4	4	14

The numbers are too small to justify any final conclusions, but the impression is left that children under ten years of age respond better than those in later childhood. It is probable that this applies to other forms of treatment in juvenile asthma where the history is necessarily of shorter duration.

Only eight out of twenty-four asthmatic children were of allergic stock. The average age of onset of asthma in these eight children was 5·2 years, as compared with the remainder of the series whose average age of onset was 4·4 years. As far as this goes, it gives no support to the belief that a history of allergic heredity determines an earlier onset in childhood.

Conclusions.

1. Twenty-four asthmatic children received five injections each of 10 c.c. of their own blood. Observations over a period of six to twelve months afterwards indicated that in approximately three-quarters the frequency of attack was appreciably reduced, while in every instance some alleviation in severity was manifest.

2. Subsidiary observations were:—

(a) That the operation of tonsillectomy and removal of adenoids in childhood is alone capable of causing a remission of seizures for as long as twelve months.

(b) That the average age of onset of the asthma in this series was no earlier in children whose blood relatives had suffered similarly.

(c) That the results of haemotherapy seemed more favourable in children under the age of ten years.

(d) That the presence of skin sensitivity to the scratch method favoured better results from autohaemotherapy than its absence.

Case records.

Case 1.—T.W., a boy aged 7, had asthma for six years. His uncle and aunt were similarly affected. He showed some chest deformity and positive skin tests to pollens, dust, feathers, kapok and animal hair. Before treatment he was having attacks about every two months, lasting two days. After treatment his mother stated that 'he had improved beyond all expectation' and that though he had occasioned colds, no attacks were observed for the first six months. Two slight attacks occurred after twelve months. (Class I, group I.)

Case 2.—E. B., a boy aged 5, had asthma for eighteen months. His grandfather and uncle were also asthmatic. He was a thin child with bronchitic signs and showed positive skin tests to dust and kapok. Before treatment he was having attacks about every month, which were severe and lasted for twenty-four hours. After treatment he had only three slight attacks in ten months. (Class I, group II.)

Case 3.—A. P., a girl of 12, had asthma for ten years. Attacks occurred most generally in the stone-fruit season, when they occurred almost weekly and lasted for two days. Otorhinolaryngological examination revealed small polypi (right antrum wash-out showed pus). Skin tests for house dust and kapok were positive. After treatment she had one severe attack six months later, but no further attacks. The mother said that it was her 'first summer without attacks since she was a young baby.' (Class II (doubtful: a. seasonal, b. antrum), group I.)

Case 4.—W. R., a boy of 6, had asthma for four years. He was a thin child with bronchitic signs and had attacks about every three weeks (though sometimes weekly) which commenced by sneezing and lasted twenty-four hours. The attacks were generally provoked by cold winds. X-ray examination of his chest suggested the possibility of bronchiectasis at the right base. Skin tests were negative. For two months after treatment the child was free from attacks and the mother stated that it was the 'longest spell for three years.' After six months there had been some sneezing attacks, but no further asthma. The first mild asthmatic attack occurred nine months after treatment. (Class I, group II.)

Case 5.—J. B., a boy of 12½, had asthma for nine-and-a-half years. A maternal aunt and a paternal uncle were similarly affected. The tonsils were enlarged, breath sounds harsh, and there was evidence of antritis. (Tonsils and adenoids were removed one month before the injections were begun.) Heavy meals, especially pastry, seemed to cause attacks and skin tests to house dust and plantain were positive. Attacks occurred every two weeks and lasted from two to three days. After treatment there was one mild attack in five months, then the most severe attack for two years. The child was still sniffling and had some nasal discharge. A year later there were four more severe attacks within eight months. The mother stated that the attacks now 'lasted only one day instead of two or three days.' (Class I, group II or III.)

Case 6.—F. O., a boy of 9, had asthma for four years. The right antrum was opaque. Skin tests were negative. Before treatment there were two attacks in six months, the attacks lasting for two days. The child seemed to have a slight attack after each injection. After treatment he had slight attacks about every two months for six to eight months, then the attacks became as bad as before. The course of treatment was repeated. (Class II, group III or IV.)

Case 7.—A. R., a boy of 10, had asthma for nine months, which seemed to be caused by cold, dry winds. There were marked chronic bronchitic changes and the tonsils were infected): (they were removed two months after the injections were given). Attacks before treatment occurred about every two months and lasted a week. Dating from the first injection, there were no attacks for six months. Then there was slight wheezing and two bad attacks and four slight attacks in the twelve months following the last injection. (Class I, group II or III.)

Case 8.—A. M., a boy of 11, had asthma for seven-and-a-half years, the attacks occurring mostly in summer. He showed some permanent changes in the chest, increased hilar markings and positive skin tests to kentucky blue and dust. After treatment there were six attacks in three months; the attacks were less severe and frequent than before. A second course of treatment was given at the end of four months; there was one slight attack in the following two months. In this instance the injections were given early in the summer. (Class I, group II.)

Case 9.—N.W., a boy of 8, had asthma for seven years, probably caused by grasses and kapok. Skin tests were positive to kapok, linseed, kentucky blue and dust. Examination of the chest revealed well-marked chronic bronchitis. Before treatment attacks occurred weekly and lasted for one or two days. Following treatment the child had only three slight attacks in seven months; the mother stated that he was 'greatly improved.' (Class I, group I.)

Case 10.—H. H., a boy of 9, had asthma for five years, the attacks being worse in winter. The breath sounds were harsh and there were small tonsillar tags. Skin tests were positive for house dust, horse dandar, kapok, plantain and cape weed. Before treatment attacks lasting two days occurred about every two weeks. After treatment there were only four slight attacks in seven months. The mother stated that the child was '90 per cent. improved.' (Class I, group I.)

Case 11.—E. B., a girl of 9, had asthma for twelve months. She seemed to be affected by dusty rooms and the skin test to house dust was positive. Examination revealed chronic bronchitis and enlarged hilar glands. Tonsils and glands were enlarged: (tonsillectomy was performed). The attacks occurred every two months and lasted for two days. During the course of treatment the child had six very slight attacks; in the seven months following treatment there were twelve slight attacks. The mother reported that her general health was greatly improved. (Class I, group II.)

Case 12.—A. H., a boy of $15\frac{1}{2}$, had asthma for ten years; the attacks occurred almost weekly and lasted for two days. There was well-marked chronic bronchitis, but no other signs. During the treatment three attacks occurred, but there were no attacks in the two months following. The boy gained 11 lb. in weight. (Class I, group I.)

Case 13.—M. H., a girl of 9, had asthma for four years. An uncle was similarly affected. The attacks occurred in spring or early summer and skin tests to kentucky blue and house dust were positive. Examination of the chest showed an increase in hilar shadows towards the right upper lobe. Attacks occurred four times a year and lasted for two days. After treatment there were no attacks for four months (autumn); there was one attack in the next two months. The mother said that the girl's health had greatly improved since the injections. (Class II, group I.)

Case 14.—E. T., a girl of 14, had asthma for eighteen months. Her father was similarly affected and also one sister, mentioned in this series. Her tonsils were unhealthy and x-ray examination of the chest showed slight fibrosis. The attacks were worse in winter, but skin tests were negative. After treatment there were no attacks for six months. (Class I, group I.)

Case 15.—N. R., a girl of 16, had asthma for ten years. There were some chest changes and the left antrum was opaque. Skin tests for horse dander and house dust were positive. Before treatment attacks had occurred nightly for two months. In the six months following the commencement of treatment there were only two attacks. The mother stated that the girl had gained considerably in weight. (Class I, group I.)

Case 16.—B. B., a boy of 12, had asthma all his life. He showed slight increase in lung markings towards the bases and positive skin tests to house dust and flock. Attacks occurred monthly and lasted a week. There were no severe attacks in the six months following the beginning of treatment. (Class I, group I.)

Case 17.—A. C., a boy of 10, had asthma for six years. There was well-marked chronic bronchitis and the nasal septum was enlarged. The skin test for plantain was positive. Before treatment attacks occurred about every two weeks and lasted for two days. There were three severe attacks during the two months of treatment. (Class I, group III.)

Case 18.—D. E., a girl of 6, had asthma for four years. X-ray examination of the chest revealed chronic bronchitic changes at both bases. Attacks had been less severe in the twelve months before treatment. There were frequent slight attacks during treatment and for the month following. Four months after

injections mother states 'better than ever been.' (Class I, group II.)

Case 19.—B. W., a girl of 16, had asthma for four years. She was thin and nervous and suffered from middle-ear deafness. Before treatment attacks occurred almost nightly. In the two-and-a-half months following beginning of treatment there were two very mild attacks; in the next six months there were six attacks; then the attacks became as bad as before. Class I, group III.)

Case 20.—M. B., a boy of $7\frac{1}{2}$, had asthma for three years. His brother and maternal grandfather were similarly affected. He had frequent colds and showed positive skin tests to kentucky blue and plantain. Attacks occurred every three or four weeks. There were no attacks during the month following the commencement of treatment. (Class I, group ?.)

Case 21.—W. B., a boy of 9, had asthma for three years. Members of his mother's family were similarly affected. The attacks were worse in summer and the skin test for house dust was positive. Examination revealed minor bronchitic changes and mucosal thickening of the right antrum. Attacks occurred at less than monthly intervals and lasted from three to seven days. In the two months following the first injection there were five shorter attacks; then for two weeks there were no attacks; after which the attacks became as frequent and severe as before. The mother said that there was ' probably a little improvement.' (Class I, group III.)

Case 22.—G. B., a girl of 9, had asthma for eight years. She showed marked bronchitis, possibly bronchiectasis, and positive skin tests for kapok, plantain, horse dander and duck feathers. Before treatment the attacks occurred every three months or less and lasted for three days. There were three mild attacks in the two months after the first injection. The mother reported that she was ' a lot better ' and that the attacks were not so frequent or severe. (Class I, group II or III.)

Case 23.—A. S., a boy of 8, had had three or four bad attacks only. His grandmother was similarly affected. He showed slight chronic bronchitis and skin tests were negative. The attacks had been some weeks apart and lasted for three days. There were no attacks in the month following the first injection. (Class I, group ?.)

Case 24.—T. E., a boy of 14, had asthma for seven years, the attacks being worse in early spring. The skin test for kentucky blue was positive. Attacks occurred about six-monthly and lasted only one day, but were severe. There was no attack in the six months, including the spring, following the first injection. (Class I, group I.)

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KETOGENIC DIET IN PERSISTENT PYURIA

BY

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The ketogenic diet as a treatment of persistent pyuria was first introduced by Clark and Helmholz in 1931[1]. They found that when the acidity of the urine was increased below pH 5·4 the urine became bacteria-free in a short time and in conjunction with this the pus disappeared from the urine. Later Clark[2] (1932) demonstrated that this sterilization was not due to the acidity of the urine. In 1933 Fuller[3] showed experimentally that the principal factor inhibiting the growth of bacteria in the urine was due to the alpha-beta-hydroxy-butyric acid. This ketone body is inactive at a reaction more alkaline than pH 5·6. Gray[4] has reported that he found the ketogenic diet helpful in pyelitis caused by staphylococci. Bell[5] discussed the value of the diet as a therapeutic measure. Clark[6] reported beneficial results in every one of fifty-three cases which he treated. Rennie[7] on the other hand in six cases of pyelitis in children found that ketogenic diet cured two, caused temporary cessation of symptoms with later relapse in three, and was valueless in one. He cites a cure in one adult case. He considers ketogenic diet of little value as a curative agent in pyuria associated with an abnormality of the urinary tract.

Since the spring of 1932, fourteen cases of persistent pyuria have been treated by means of the ketogenic diet. The ages of the children, all girls, were from four to twelve years. In this present series there were three children with bilateral hydronephrosis, one with a prolonged pyuria but no anomaly, while the remainder had a unilateral hydronephrosis. All those with an anomaly had an obstruction either at the uretero-vesical orifice, in the ureter or at the pelvo-ureteral junction due to an aberrant artery. One child had a left renal calculus as well.

The routine followed was that outlined by the Mayo Clinic[8]. The patients were started on a $\frac{\text{fatty acid}}{\text{glucose}}$ ratio $\frac{1{\cdot}6}{1}$ and over a period of a week the ratio was increased to $\frac{3{\cdot}0}{1}$. In a few cases this ratio was increased to $\frac{3{\cdot}3}{1}$. Later cases were given ten grains of ammonium chloride three times a day to hasten the formation of an acid urine. When possible these cases were discharged from the hospital on a modified ketogenic diet which consisted of low percentage vegetables and fruits, no bread, sugar, pastry, candy; bran substitutes for bread stuffs; normal protein and high fat consisting of half a pint of 32 per cent. cream and a liberal allowance of butter.

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Urines were cultured frequently, bacterial counts made and the urinary pH determined by the colorimetric method. The bacterial species found in this group of cases included B. coli, B. coli communior, Bacillus dispar, staphylococcus haemolyticus and non-haemolyticus, C. xerosis and streptococci.

Before the introduction of the ketogenic diet, surgical treatment was used as the treatment of persistent pyuria. This consisted of dilating or removing the cause of obstruction which allowed the kidney to drain more freely. In chart I is seen the effectiveness of surgical treatment in seven cases, over a period of eight months to four years. In these cases the hydronephrosis had not increased in size in any case, and in the majority it was either smaller or had disappeared. In one case there was a recurrence of the pyuria and in all cases there was bacilluria. In hope of

CHART I.

NAME	AGE IN YEARS	ANOMALY	DURATION OF ILLNESS PREVIOUS TO TREATMENT	TREATMENT	BACTERIAL SPECIES	FOLLOW-UP
M. R.	4	Rt. hydronephrosis, stricture rt. ureter	3 mth.	Surgical dilation of rt. ureter	B. coli communior to b. dispar	In 4 yr. hydronephrosis disappeared, urine culture positive for micro-organisms. No pus cells
G. G.	6	Bilateral hydronephrosis bilateral ureterovesical obstruction	3 mth.	Surgical	B. coli	In 4 yr. left side normal, rt. side has decreased. Culture urine, b. coli. Occasional pus cell
F. S.	6	Rt. hydronephrosis, obstruction rt. ureterovesical orifice	18 mth.	Surgical	B. coli	In 3 yr. hydronephrosis no larger. Urine culture positive and still contains pus cells
H. C.	4	Rt. hydronephrosis, obstruction rt. ureter	2 mth.	Surgical	B. coli to b. coli communior	18 mth. after surgical treatment hydronephrosis smaller. Urine positive and recurrence of pyuria
M. B.	5	Rt. hydronephrosis due to double rt. ureter	2 mth.	Surgical	B. coli to b. coli communior	3 yr. later occasional pus cell in urine; hydronephrosis not as large. Urine culture positive
R. K.	3	Rt. hydronephrosis, obstruction rt. ureterovesical orifice	3 wk.	Surgical	B. coli communior	2 yr. later very slight hydronephrosis, no pus in urine. Urine positive for bacteria
D. M.	4	Rt. hydronephrosis, aberrant vessel. Left renal calculus	3 mth.	Surgical	B. dispar to streptococci	8 mth. later left hydronephrosis no larger. Culture urine positive

clearing up this bacilluria, four of the seven children were placed on the ketogenic diet (chart II). Two of these children did not become bacteria-free. One child became bacteria-free in six month's time and has remained so for twelve months. The other child became bacteria-free in seven days but had a recurrence eight months later of pyuria with bacilluria.

Chart II.

Name	Treatment	Duration of ketogenic treatment in hospital	Range of pH	Time for bacteria free	Duration of treatment in out-patient department	Follow-up
H. C.	Dilatation of obstruction. 18 mth. later put on ketogenic diet	13 days	5·4-5·2 from onset	7 days	No treatment for 8 mth. then modified ketogenic diet	8 mth. after discharge from H. S. C. no treatment. Urine bacteria free. At this time recurrence of pyuria and bacilluria. Modified ketogenic diet for 10 mth. No recurrence of pyuria. Occasional pus cell in urine and bacteria present in urine
M. B.	Relief of obstruction. 3 years later put on ketogenic diet	10 days	6·8-5·6	not free	Modified ketogenic diet for 10 mth.	In 10 mth. pH of urine never below 5·6. No symptoms. Urine, occasional white cells. Bacteria still present.
A. K.	Obstruction dilated. Put on ketogenic diet 22 months after dilation	8 days	6·4-5·4	not free	Modified ketogenic diet for 11 mth.	In 11 mth. pH of urine 5·8-6·2. No symptoms. No pyuria. Urine still bacteria positive
D. M.	Relief of obstruction. 8 mth. later put on ketogenic diet	16 days	7·6-5·4 in 16 days	Bacilluria for 6 mth. then sterile	Modified ketogenic diet for 12 mth.	In 12 mth. no pyuria, no bacteria and no symptoms

Chart III shows the results of the ketogenic diet in ten children who had no previous surgical treatment. In nine of these cases the urine became sterile. In the one patient's urine that did not become sterile there was a mixture of bacteria and though the B. coli were killed in thirty-four days the staphylococci persisted. That there is a definite relationship between the acidity of the urine and its bactericidal effect is clearly seen in charts II and III. The urine did not become bacteria-free till the urinary pH became 5·4. It took from one to twelve days to obtain this degree of acidity, but as a rule the time required was from four to six days. Sterile urines were obtained in from two to seven days except in three cases when it was found necessary to prolong the diet over a considerable time. One of these patients became bacteria-free in seventy-four days, one in four months

CHART

Name	Age in years	Anomaly	Duration of illness	Previous treatment	Later treatment	Duration of treatment in hospital
E. H.	8½	Rt. hydronephrosis, obstruction rt. ureter	4 mth.	None	Ketogenic diet	7 days
A. M.	4½	Rt. hydronephrosis, obstruction rt. ureter	2 yr.	None	Ketogenic diet and ammon. chloride	4 days
M. C.	6	Left hydronephrosis, obstruction left ureter	2 days	None	Ketogenic diet	10 days
J. M.	3¾	Bilateral hydronephrosis, obstruction uretero-vesical orifices	2 yr.	None	Ketogenic diet and ammon. chloride	40 days
M. L.	8	Rt. hydronephrosis, obstruction rt. ureter	1 yr.	None	Ketogenic diet	28 days
M. B.	11	Prolonged acute. No anomaly	3 days	None	Ammon. chloride and ketogenic diet on 30th day of illness	25 days
M. L.	10	Bilateral hydronephrosis, obstruction uretero-vesical orifices	4 yr.	None	Surgical and ketogenic diet	1 mth.
D. H.	12	Bilateral hydronephrosis, obstruction uretero-vesical orifices	1 yr.	None	Surgical and ketogenic diet	42 days
M. M.	6	Left hydronephrosis, obstruction at junction of double ureters.	2 wk.	None	Ketogenic diet and ammon. chloride	10 days
L. M.	9½	Rt. hydronephrosis, obstruction rt. ureter	6 days	None	Ketogenic diet	10 days

III.

Duration of treatment in out patient department	Bacterial species	Range of pH	Time for bacteria free	Follow-up
Mod. ketogenic diet 6 mth. with ammon. chloride	Staph. aureus	6·0-5·4 in 1 day	Intermittent bacilluria for 4 mth.; then sterile	2 mth. later no symptoms. No pyuria, no bacteria
Mod. ketogenic diet with ammon. chloride	Staph. aureus	6·6-5·4 in 4 days	2 days	8 mth. later no pyuria, no symptoms, no bacteria
Ammon. chloride	B. coli	5·4-5·2 from onset	6 days	6 mth. free from pyuria and bacteria, then recurreace of pyuria
None	Staph. aureus and b. coli communior	6·0-5·4 in 12 days	34 days B.coli comm-unior gone. Staph. remained	3 mth. later occasional pus cell in urine and staph. present in urine
None	B. coli	6·4-5·4 in 6 days then 5·2-5·4	11 days	18 mth. later no pus cells. Urine sterile
None	B. coli	6·6-5 8 in 12 days	21 days	1½ mth. later no pus in urine and urine sterile
Mod. ketogenic diet 6 mth.	Staph aureus haem. and strept. faecalis	5·4 from onset	Staph. dis-appeared in 9 daysand strept. faecalis 74	In 12 mth. no symptoms, no pyuria, urine sterile
Mod. ketogenic diet 1 year	Staph. aureus haem. C. xerosis. After 1 mth. b. coli communior	8·4-5·4 in 6 days	Staph. gone 8 days. C. xerosis 7 days. B. coli communior 6 days	In 18 mth. no symptoms, occas-ional pus cell in urine. No bacteria
Mod. ketogenic diet for 4 mth.	Staph. aureus, haem. Staph. aureus non haem. C. xerosis	6·2-5·2 in 1 day	6 days	No symptoms, no cells, no bac-teria after 8 mth.
Mod. ketogenic diet for 5 mth.	Staph. aureus	5·8-5·2	5 days	No symptoms, no cells, no bac teria after 8 mth.

and the other in six months. In three patients the urines did not become bacteria-free, but in one of them this was due to the fact that her urine pH did not go below 5·6 and she was discharged before a more acid urine could be produced. In regard to the second of these three children, though the acidity reached pH 5·4 she still had a bacilluria eleven months later. The third case had both staphylococcus and b. coli in the urine and, although the b. coli disappeared in thirty-four days, the staphylococcus was present on the patient's discharge from hospital and also three months later when she was re-admitted. In conjunction with sterile urine the pus cells usually disappeared.

Following discharge from the hospital these cases were followed in the out-patient department over periods of from two to eighteen months. Some of these children were sent home on a modified ketogenic diet as has already been described.

Generally speaking, the health of these children has been very good. Most of them have gained weight and have had the minimum of upper respiratory tract infection. The three children who did not become bacteria-free in hospital have had a persistent bacilluria up to the present, though one gives consistently negative results for examination for albumin and pus cells while the third still shows occasional pus cells. This child had also had dilatation of her obstruction and one year later the hydronephrosis had decreased considerably in size. The other case has already been described above. In the remaining eleven cases the patients have had sterile urines over a period of two to eighteen months, but in two of these cases there was a recurrence of pyuria over a period of six months and eight months in which there were numerous pus cells and bacteria again present in the urine. In addition, an unsuccessful attempt was made to treat two infants fourteen and four months of age. This was due to their inability to tolerate the high fat diet.

Comment.

To compare the ketogenic diet with the surgical treatment of this type of case is difficult as the principle of surgical treatment is to relieve the obstruction to allow free drainage and to reduce the pressure atrophy on the kidney, aiming at some restoration of kidney tissue if no further obstruction occurs. With this treatment[9] these children usually do well but in seven patients who have had their urine cultured for from eight months to four years after the relief of the obstruction, micro-organisms were still found to be present. With ketogenic diet and the production of sterile urine it can well be argued that kidney infection is eliminated but just how rapidly or to what extent the hydronephrosis will progress is not known. This will have to be controlled with further intravenous pyelography and cystoscopic examinations. That this form of treatment is not always effective is shown by the fact that 21 per cent. did not become bacteria-free, though one case was not under observation long enough for a fair trial. In 14 per cent. there

was a recurrence of the pyuria in six months and eight months and in the remaining 65 per cent. of cases the results are good.

Surgical treatment of chronic pyelitis serves merely to relieve the anatomical irregularity with the idea that the establishment of adequate drainage will remove the focus of infection. No bactericidal principle is provided to hasten the return of proper healthy function. The ketogenic diet does not correct anatomical anomalies but does provide the bactericidal agent. From a study of the two types of treatment it would appear that a combination is to be recommended to obtain the best results.

Conclusions.

By means of the ketogenic diet urine can be made both bacteria- and pus-free in 65 per cent. of the chronic pyelitis cases. This had been tested over periods ranging from two to eighteen months.

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